American Journal of Diseases of Children

VOLUME 76 DECEMBER 1948 NUMBER 6

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ACTION OF INTRAVENOUS INJECTIONS OF HISTAMINE ON THE BLOOD OF HEMOPHILIC CHILDREN

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DURING the treatment of adults for migraine with intravenous injections of histamine,[1] it was observed that the qualitative platelet activity was increased. In this earlier study data on 15 patients who received intravenous injections of histamine for migraine were obtained. Blood was drawn before onset of each injection, using the technic of Sanford and Leslie.[2] This blood was collected in chilled syringes, counted on a chilled counting chamber and centrifuged in waxed chilled tubes. The coagulation times for whole blood, cell-free plasma and platelet-free plasma were determined. Hematocrit readings and platelet counts were made simultaneously.

The histamine was given at a constant rate of 20 drops per minute in 500 cc. of isotonic sodium chloride solution. The quantity of histamine was doubled with each injection, 0.2 mg. being used for the first injection and 2.0 mg. for the last. The results of these determinations are presented in chart 1. In this chart the coagulation time of plasma A, which represents plasma containing its full quota of platelets without centrifugation, is indicated by a dotted line and the coagulation time of plasma B, which represents the platelet-free plasma obtained by centrifugation, by a solid line. It will be seen that no change in the total number of the platelets occurred during the course of the injections of histamine. However, in the coagulation of the plasma fractions, it will be observed that a decrease in the coagulation time of the whole plasma fraction was caused by a decrease in the coagulation time of the platelet-free plasma fraction, which is an index of the activity of the platelets.

From the Presbyterian Hospital and the Department of Pediatrics, Rush Presbyterian Division of the University of Illinois.

1. Butler, S.; Thomas, W. A., and Sanford, H. N.: Blood Coagulation During Intravenous Injection of Histamine, J. Lab. & Clin. Med. **32**:1432 (Nov.) 1947.

2. Sanford, H. N., and Leslie, E. I.: An Improved Method for the Estimation of Quantitative and Qualitative Platelet Factors, J. Lab. & Clin. Med. **27**:255 (Nov.) 1941.

This resulted in a small but definite decrease in the coagulation time of the whole blood. The decrease was from 1.0 to 1.9 minute in every instance.

It must be remembered that these 15 persons all had normal blood coagulation factors, and, as is well known, it is difficult to alter the blood coagulation to any appreciable extent in normal persons. Inasmuch as the decrease in the coagulation time of this normal blood appeared to be entirely due to an increased platelet activity (qualitative platelet function), it was decided to try the effect of histamine injections on the blood of persons with active hemophilia, inasmuch as their blood coagulation is apparently deranged by abnormal qualitative platelet defects.

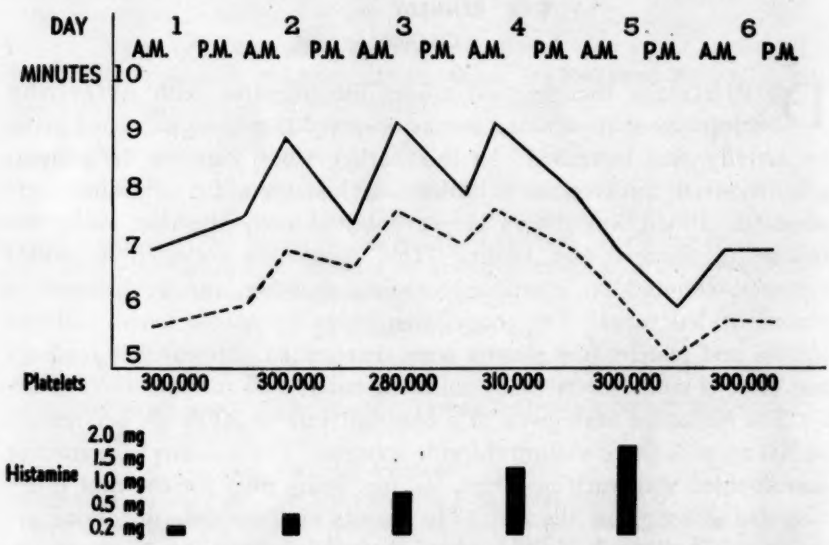

Chart 1.—Graph showing action of intravenous injections of histamine on platelet activity in 15 adults with migraine. Coagulation time of plasma A (uncentrifuged plasma with full number of platelets) is indicated by the broken line. Coagulation time for plasma B (platelet-free plasma obtained by centrifugation) is indicated by the solid line. The lower portion of the chart shows the change in platelet count per dose of histamine.

The first patient with hemophilia to whom histamine was given was a Negro boy, 7 years of age. He had been treated at the hemophilia clinic for the past two years. His bleeding activity came in cycles of about every four months and was characterized by bleeding from the mouth and gastrointestinal tract and subcutaneous hematoma. His normal blood base line with no bleeding activity showed the coagulation time of whole blood to be 20 minutes, of plasma A (containing platelets) 20 minutes and of plasma B (platelet-free) 35 minutes. On this admission he had been bleeding from the mouth and rectum for two days and had symptoms of meningeal irritation. He had had one similar episode of bleeding six months before with symptoms of meningeal hemorrhage. His time for whole blood coagulation was 30 minutes, for plasma A 40 minutes and for plasma B 45 minutes; total platelets numbered 320,000. The results are shown in chart 2.

Inasmuch as we were somewhat uncertain of the amount of histamine to give a child this age, one injection of 0.3 mg. was administered. Four hours later his bleeding ceased; coagulation time for plasma A fell to 30 minutes and for plasma B to 37 minutes, with no change in total number of platelets. Twelve hours later there was still no bleeding, but coagulation times for both plasma fractions had risen in a somewhat alarming fashion to 43 minutes for plasma A and 90 minutes for plasma B. The dose of histamine was increased to 0.4 mg., and within two hours the time for plasma A had fallen to 40 minutes and for plasma B to 42 minutes. The following morning the time for plasma A had fallen to 21 minutes and for plasma B to 32 minutes. The values rose again the following day and 0.5 mg. of histamine was given. Again they fell, but since they were above his normal level, 0.6 mg. was given the following day. His coagulation time for plasma A now fell to

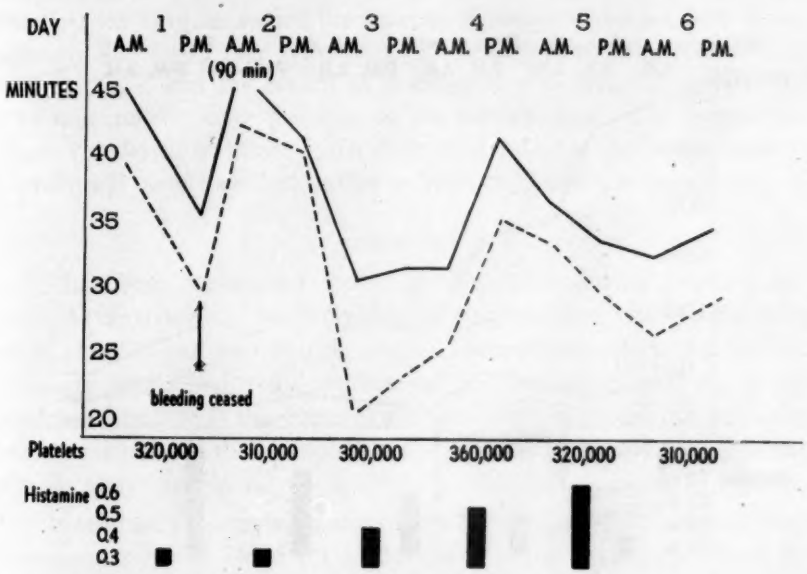

Chart 2.—Graph showing action of intravenous injections of histamine on coagulation times of a boy, aged 7 years, weighing 42 pounds (19.1 Kg.), with hemophilia in an active cycle. Coagulation time for plasma A is indicated by the broken line and coagulation time for plasma B by the solid line. The lower portion of the chart shows the change in platelet count per dose of histamine.

26 minutes and for plasma B to 30 minutes, continuing at this level throughout the following week, when he was discharged. His total platelet count varied from 280,000 to 400,000. He has not returned to the clinic for six months. After the third injection of histamine his sensorium began to clear, and he was quite normal by the end of the fifth injection. He was apparently entirely recovered on his discharge from the hospital.

During the next four months 5 boys with hemophilia were treated in this manner. Their respective ages were 16 months and 4, 5, 6 and 7 years. All the boys, with the exception of the 16 month old child, had been followed in our hemophilia clinic for at least two years.

This boy was studied for two weeks in the hospital, and his normal base line with no bleeding activity was determined during his first episode of hemorrhage, which subsided spontaneously. On this discharge his bleeding time was 21 minutes, plasma A coagulation time 31 minutes and plasma B coagulation time 35 minutes. On his return to the hospital two months later the coagulation time of whole blood was 48 minutes, of plasma A 59 minutes and of plasma B 65 minutes. He was bleeding from the mouth and nose, and his history included a fall. The next day these values had increased to coagulation time of 56 minutes for whole blood, 102 minutes for plasma A and 300 minutes for plasma B. He was judged to be in an active cycle of bleeding and histamine was given in amounts of 0.2, 0.4, 0.6, 0.8 and 1.0 mg. Visible bleeding ceased after the second injection, with a coagulation time of 30 minutes for whole blood, 30 minutes for plasma A and 42 minutes for plasma B. At the end of treatment his coagulation time for whole blood was 20 minutes, for

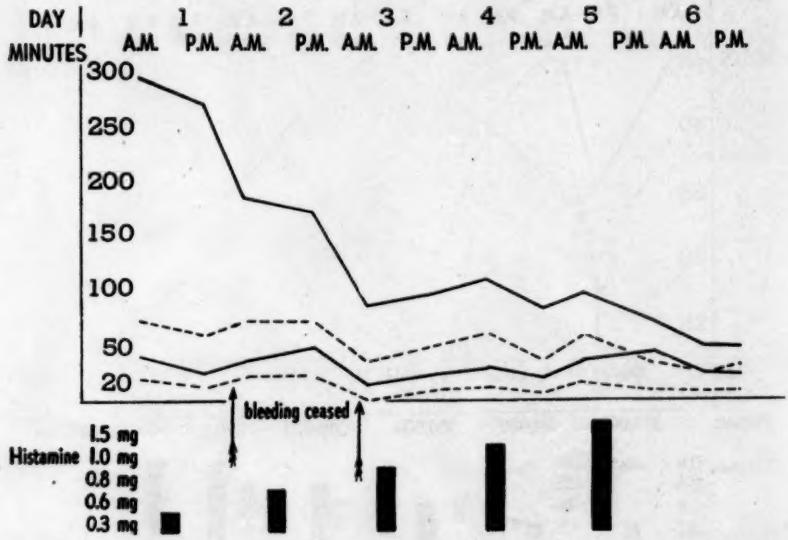

Chart 3.—Graph showing averages for activity of intravenous injections of histamine on coagulation times of 5 boys with hemophilia in an active cycle. Plasma A coagulation time is indicated by the broken line and plasma B coagulation time by the solid line.

plasma A 30 minutes and for plasma B 35 minutes. However, owing to a delay in bringing him to the hospital after the accident, he was so anemic (hemoglobin concentration, 4 Gm., 1,800,000 red blood cells, and 17,000 white blood cells, with 280,000 platelets) that 500 cc. of type 0 blood was given to him. This resulted in a coagulation time for whole blood of 5 minutes, for plasma A of 14 minutes and for plasma B of 18 minutes.

Three months later he returned with bleeding from his mouth and nose. This time he was in good condition, and his whole blood coagulation time was 28 minutes, plasma A time 32 minutes and plasma B time 38 minutes. The following day it was 22 minutes for whole blood, 30 minutes for plasma A and 35 minutes for plasma B. He was judged to be on an inactive or improving cycle and nothing was done for him. The following day bleeding ceased. He has not returned to the clinic since.

The other 4 boys had been studied in our hemophilia clinic from two to five years and had well established normal base coagulation values. One was judged to be on a descending cycle and was not treated until his appearance again three months later, when he was on an ascending phase. The others were all in active cycles of bleeding. These were given histamine in amounts of 0.3, 0.6, 0.8, 1.0 and 1.5 mg. All responded with cessation of bleeding after the first or second injection, with a corresponding decrease in the coagulation time of the whole blood, plasma A and plasma B. One boy, 5 years of age, became flushed and complained of headache after the last 1.5 mg. injection of histamine. These signs ceased at once on injection of 200 mg. of vitamin C. Since that time we have decreased the amount of histamine to not over 1 mg. and have had no further symptoms. No other symptoms were noted in these patients, and the return of a sense of well-being in each of the boys was noticed after the first or second injection. The coagulation values are shown on chart 3. In none of these boys was any change in normal total platelets noted during or after the histamine injections.

COMMENT

It has been recognized for some time that during peptone and anaphylactic shock and in thrombopenic purpura simultaneous clumping out of platelets and vasodilation occur. Theoretically, since platelets are no longer available for the removal of free histamine from the blood, this free histamine is the cause of the vasodilation. Some investigators, however, expressed the opinion that the platelets themselves are a source of some body histamine.

We originally attempted to discover whether a continuously high level of histamine in the blood for many hours would materially affect the total quantitative platelets of the blood, either by driving them out of the free circulation or by causing their increase in an attempt to overcome the increased histamine concentration. Such an effect we absolutely failed to produce. In no instance did any appreciable lowering occur, nor, in fact, was there any change in the total platelet quantity, either in the normal person or in the person with hemophilia.

To our surprise, the coagulation time of the blood was lowered, slightly it is true in the normal person, but considerably in the hemophilic patient, caused, not by any change in the quantity of the platelets, but by an increase in their disintegration ability, or a qualitative change. This was of short duration in the blood of the normal person, ceasing almost as soon as the histamine was withdrawn, but it persisted in the person with hemophilia for some time at least. It was not permanent in the hemophilic patient, inasmuch as 2 of the boys treated returned

with increased time of blood coagulation owing to a lessening in the disintegration of the platelets after three months. It is of interest that each of these episodes was of much shorter duration than the former ones, the platelet disintegration was not as delayed as usual, and no treatment was necessary. However, anyone who has worked with persons having hemophilia will realize that these instances are well within the chance of accidental occurrence.

We do not know the reason for this action. Inasmuch as it does not take place in vitro, it must cause a change in other tissues of the body rather than in the circulating platelets. Whether this action is on the platelets themselves or on some heretofore unknown circulating inhibitory substance is only conjecture. However, as we are not aware of the existence of such a hypothetic substance, it would be more likely that histamine acts in some way on new platelets forming in the hematopoietic organ and that these act like normal platelets in disintegration ability and not like hemophilic platelets. Some basis is given for this idea by the fact that it takes forty-eight hours or more for an appreciable change in the qualitative action of the platelets to be seen, and, inasmuch as the life cycle of the platelets is assumed to be four days, this would give time for new platelets formed to carry this ability of disintegration into the blood coagulation system.

Many new avenues of thought are opened up by this problem. Will other histamine-like substances cause the same reactions? What is the action of antihistamine-like substances on the platelets? These questions are now being studied by us, but the lack of subjects, who must show an active hemophilic bleeding cycle, makes this work so slow that we present it for others to study.

We hesitate to present this material as treatment for hemophilia. The medical literature is full of treatments for this condition that apparently were successful because they were used on persons with hemophilia in a recovery cycle when anything would apparently cure the condition. Histamine has decreased the coagulation time of the blood of all hemophilic patients that we treated. We know, however, of one instance in another clinic in which, while histamine stopped the bleeding, it did not bring the coagulation time down to the normal base value for that patient. We do feel that this treatment may offer another method to hasten the coagulation of hemophilic blood. It is, at least, not harmful and it is sparing of blood necessary to stop the abnormal bleeding in some of these persons during an active bleeding cycle. It must be remembered that the treatment does not furnish blood. If bleeding has been severe before coagulation can be accomplished, a final transfusion must be given to return the blood to something like normal values.

CONCLUSIONS

Intravenous injections of histamine will decrease the coagulation time of the blood in hemophilic patients by increasing the platelet disintegration (qualitative activity). It has no effect on the total number of circulating platelets (quantitative action). This action is not permanent, but it is sufficient to cause a cessation of bleeding and to decrease the coagulation time of the blood to its normal value for that person, as shown by results of treatment in 6 hemophilic children.

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ENTERAL TREATMENT OF DIARRHEA IN INFANCY, INCLUDING EPIDEMIC DIARRHEA OF THE NEWBORN

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THE ENTERAL treatment of diarrhea in infancy has much to recommend it. It is simple; it can supply adequate caloric, mineral and protein intake. Moreover, it does not usually require hospitalization, with the attendant risks of cross infection. The addition of apple powder renders the time-honored minimal diet unnecessary.

EPIDEMIC DIARRHEA OF THE NEWBORN

The epidemic diarrheas of the newborn form an important group in this field. A good working definition of this syndrome was in a bulletin issued in 1943 by the California State Department of Health.[1] This bulletin defined epidemic diarrhea of the newborn as follows:

> Diarrhea shall be considered to exist when an infant has four or more loose stools in 24 hours, except in the case of entirely breast fed infants who show no other signs of illness and who are gaining weight. . . .
>
> The condition is characterized by a short prodromal period of drowsiness and lack of appetite soon followed by the second stage of the disease characterized by the occurrence of frequent watery stools, by dehydration and by varying degrees of toxicity.

I see no reason to believe that this symptom complex is a separate disease entity. It seems rather to be, from the evidence at hand, an infection modified by the immaturity of its host and differing in no other way from many of the diarrheas occurring in older infants and in adults.

From a review of the literature on epidemic diarrhea, Clifford[2] reached a similar conclusion, that

> the syndrome described as epidemic diarrhea of the newborn is not a pathologic entity but a miscellaneous group of cases of various etiologies, known and unknown, bound together by a common symptom—diarrhea.

Rotch's[3] classification of diarrheal diseases, from his book written in 1906, mentioned nervous diarrhea, intestinal indigestion of dietary origin, infectious diarrhea and cholera infantum. The present report is not concerned with the first two classes, but the third and fourth

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Read before the Section on Pediatrics at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 23, 1948.

1. California State Department of Health Bulletin, May 20, 1943.
2. Clifford, S. H.: New England J. Med. **237**:969 (Dec. 25) 1947.
3. Rotch, T. M.: Pediatrics, Philadelphia, J. B. Lippincott Company, 1906, pp. 800-826.

are of interest. Rotch included in the infectious class those cases in which a definite bacterial factor could be isolated. The fourth class, cholera infantum, included those cases in which no organism could be consistently isolated. This group was evidently that which is now considered to be of virus origin. The cases which are now referred to as epidemic diarrhea include those which Rotch designated as infectious diarrhea, as well as those which he classified as cholera infantum.

TREATMENT

At the beginning of the century diarrheal conditions played a prominent role in the diseases of infancy. While the mortality and morbidity of intestinal infection was high in the community at large, the situation in the infant asylums became so serious that these institutions were finally abolished.

With the advent of pasteurized milk and improved hospital technic, diarrheal diseases in infancy decreased notably for a quarter of a century. During the last fifteen years, however, a new situation has arisen. Previously, the great majority of obstetric cases were managed in the patients' homes. This changed gradually until it became the general custom to take nearly all such cases to the hospital. The obstetric nursery was the natural consequence. It is here that trouble lies. Will the obstetric nurseries be obliged to close as the infant asylums were?

The treatment of the severe diarrheas has been more or less standardized in the various hospitals. The main objective of this treatment is the correction of the dehydration and the disturbances of the acid-base equilibrium. This is a proper objective and is usually attained by intravenously administered therapy, the details of which are familiar. I will not go into this phase of the problem other than to state that therapy is often continued intravenously for weeks before the institution of oral feeding.

There is another phase which I do wish to discuss, however. This phase is best illustrated by a quotation from an article by Glynn.[4] Under the heading "Relief of the Diarrhea" is this passage:

> Checking the diarrhea itself is best achieved by giving the patient nothing by mouth. Starvation is continued until the infant stops passing stools for at least twelve hours, or longer if necessary. Usually the frequency of stools decreases markedly during the period of starvation. The duration of starvation is usually twenty-four to thirty-six hours, but occasionally longer.
>
> The decision to begin feeding by mouth is of critical importance, and must be individualized in each case. One requirement is absence of stools for twelve or twenty-four hours. The more severe or prolonged the diarrhea was, the longer should be the period free from stools before resuming oral feeding.

4. Glynn, M. J.: J. Pediat. **29**:205 (Aug.) 1946.

Such a schedule of treatment has been rather generally followed in larger institutions during the last few years. Glynn referred to the period of treatment given intravenously as lasting from twenty-four to thirty-six hours. It has, however, been continued in some institutions for weeks before the desired cessation of diarrhea seemed to indicate that the time for resumption of oral feeding had arrived. There has recently been a trend away from the prolonged intravenous administration of therapy. Except for infants with extreme dehydration or severe vomiting, oral feeding is now more generally practiced.

The following oral feeding is typical of that currently used, either initially or after a preliminary course of treatment given intravenously.

First, a potassium solution such as that recommended by Darrow,[5] or some modification[6] thereof, is used. This is usually given in a 10 per cent dextrose solution. One hundred to 150 cc. per kilogram is administered by mouth until the bowel movements show improvement either in character or in frequency. This requires usually one to four days.

Then a 2 per cent milk mixture is given in sufficient amounts to supply 10 calories per kilogram of body weight. Daily increases sufficient to supply 10 calories more per kilogram are given until the infant is receiving 110 calories per kilogram from this exclusive milk diet. At the end of the second week, cereals and vegetables are gradually added. Thus, there is a minimal period of three weeks, or longer in cases in which relapses occur, during which the infants are on a diet inadequate both quantitatively and qualitatively.

These methods of treatment are fairly typical of the present day management of diarrhea in infancy. I think they are seriously at fault because they are starvation treatments.

The theory is that by such starvation the intestinal tract is given a rest and the infecting organism is deprived of nourishment. Workers are failing to remember the lesson which physicians of fifty years ago learned in the treatment of another disease characterized by intestinal infection, namely, typhoid fever. In this condition the administration of a liberal diet resulted in a dramatic change in the entire course of the disease. One must not forget to treat the patient while curing the disease.

The starvation treatment currently practiced in the diarrhea of infancy is certainly a factor in the production of ketosis and the depletion of water and minerals—conditions which one attempts to remedy by concomitant intravenous administration. Such therapy takes cognizance of the water

5. Darrow, D. C.: J. . liat. **28**:541 (June) 1942.

6. Butler, A. M., and Talbot, N. B.: New England J. Med. **231**:585 (Oct. 26) 1944.

and mineral requirements of the infant. The caloric and protein requirements are, however, usually ignored or at best unfulfilled. The consequent protein deficiency results in a depletion of antibodies and an inevitable deterioration in the resistance of the infant to infection. The aforementioned inadequate oral diet is open to the same criticism.

In this connection Cannon [7] stated:

> Inasmuch as experimental evidence indicates that globulin-production is dependent upon the intake of amino acids and is impaired by an inadequate intake of dietary proteins, it also follows that antibody-production must similarly depend upon protein-intake.

Wissler and his associates [8] wrote:

> . . . We have presented evidence indicating that severe protein deficiency, brought about by a prolonged low-protein diet, leads to a marked decrease in production of antibody.

Such observations indicate the extreme importance of an adequate protein supply in conditions such as diarrhea of infancy. In this disease, recovery depends to a great extent on maintenance of the natural defenses, namely, the antibodies. Such maintenance can be attained best and, perhaps, only by adequate oral feeding of the sick infant.

Is adequate oral feeding inadvisable or impracticable in diarrhea? I think not. These infants, at least, in the early stages of the disease, will take their formula readily. While lactic acid milk or boiled skimmed milk are often used initially in oral feedings, the ideal initial form of nourishment is apple powder.

APPLE POWDER IN TREATMENT OF DIARRHEA

The use of apple as a medicinal agent is not new. It dates back as far as biblical times. References to its use occur in the folklore of many countries. An article by Moro [9] in 1929 revived interest in this form of therapy. Many articles have appeared in the literature since that time. Birnberg,[10] in 1933, made one of the first reports in American literature. Anderson and Nelson,[11] in 1944, reported on the use of apple powder in epidemic diarrhea of the newborn.

Originally, apple was used empirically. Its therapeutic action is not yet fully understood. Its value lies in the fact that when administered in full dosage it enables the infant's digestive apparatus to tolerate and

7. Cannon, P. R.: J. Immunol. **44**:107 (June) 1942.

8. Wissler, R. W.; Woolridge, R. L.; Steffe, C. H., Jr., and Cannon, P. R.: J. Immunol. **52**:267 (March) 1946.

9. Moro, E.: Klin. Wchnschr. **8**:2414 (Dec.) 1929.

10. Birnberg, T. L.: Raw Apple Diet in Treatment of Diarrheal Conditions in Children, Am. J. Dis. Child. **45**:18 (Jan.) 1933.

11. Anderson, N. A., and Nelson, W. E.: J. Pediat. **25**:319 (Oct.) 1944.

to utilize a high calory, high protein diet, provided the sugar content is kept low.

In the administration of the apple powder, enough water is used to make a thin gruel. It may then be fed from the bottle, if the hole in the nipple is enlarged sufficiently to give a free flow of the mixture. I have used from a level to a heaping tablespoonful, equivalent to 5 and 10 Gm. respectively, of a commercial preparation of apple powder ("appella"). This mixture was fed every three hours, giving 6 or 7 feedings in twenty-four hours. The formula of boiled or evaporated milk was given immediately after the apple powder and was usually well taken and well retained, although the entire feeding amounted to 6 ounces (180 cc.) of fluid every three hours. If necessary, the bulk of the feeding may be reduced by use of a mixture of milk powder and apple powder in the amount of water which is adapted to the particular infant.

If persistent vomiting is present, or if the dehydration is severe, intravenously administered therapy may be necessary at the beginning of treatment. Oral feeding should be resumed, however, as soon as the aforementioned conditions have been corrected. In the majority of cases, oral feeding is practicable from the outset. I have used a formula suited to the age of each infant, with the exception of added sugar. This formula was rapidly increased to include whole boiled milk or equal parts of evaporated milk and water. In addition, one of the prepared barley or wheat cereals was used, as well as one of "Swift's Brand" strained meat products and a multivitamin preparation. The diet outlined supplies, for an infant weighing 4 Kg., 150 calories, 5.2 Gm. of fat, 4.2 Gm. of protein, 5.6 Gm. of carbohydrate and 220 cc. of fluid per kilogram of body weight.

During the treatment of the diarrhea, as well as during the convalescent period, it is important to keep the sugar content of the diet low. Premature resumption of sugar in the formula will result in a recurrence of the symptoms. Under this regimen, the number of movements was reduced in three to five days to three or four per day. The character of the movements in this period changed rapidly to a soft, normal appearance. The normal gains in weight and the general well-being of the infant were evidence that the food elements, water and minerals were being well absorbed and well utilized.

Support of this last observation appeared in the recent work of Chung and Holt.[12] They observed in a study of infant diarrhea that a liberal diet, as compared with a minimal or starvation diet, resulted in an increased absorption of the total ash, water, sodium, potassium, calcium, chloride, fat and nitrogen.

12. Chung, A. W., and Holt, L. E., Jr.: Rev. Pediat. **2**:503 (Aug.) 1947.

REPORT OF CASES

CASE 1.—The protocol for D. P., aged 1 month, is as follows:

Dec. 13, 1946: Had 20 watery movements with mucus.

December 14: Given "appella", 1 tablespoonful (15 cc.) every three hours, and a formula consisting of 12 ounces (360 cc.) evaporated milk and 18 ounces (540 cc.) water, 3 ounces (90 cc.) of which was given every three hours, with ½ ounce (15 cc.) barley twice a day and 3 teaspoons (15 cc.) of "Swift's Brand" strained beef.

December 17: 8 movements per day of less watery consistency; formula increased to 14 ounces (420 cc.) of evaporated milk and 16 ounces (480 cc.) water; weight, 7 pounds 2 ounces (3,232 Gm.).

December 21: 5 or 6 movements per day of more substance, becoming yellow in color; weight, 7 pounds 4 ounces (3,289 Gm.).

December 24: 5 movements per day, mushy in consistency; weight, 7 pounds 10 ounces (3,459 Gm.).

December 27: 4 or 5 movements per day, becoming firm in consistency; weight, 8 pounds (3,629 Gm.).

Jan. 3, 1947: Same number of movements; weight, 8 pounds 8 ounces (3,856 Gm.).

January 11: Movements more frequent, 6 or 7 per day; weight, 8 pounds 8 ounces.

January 18: 3 to 5 movements per day; weight, 8 pounds 14 ounces (4,026 Gm.).

January 25: 2 or 3 movements per day, normal in consistency; weight, 9 pounds 4 ounces (4,196 Gm.).

February 18: Movements normal in consistency and number; weight 10 pounds 12 ounces (4,876 Gm.).

CASE 2.—The protocol for D. H., 3 weeks of age, is as follows:

Nov. 29, 1946: Five days ago movements became loose and watery, 7 to 8 per day in number; appetite failed; weight, 6 pounds 10 ounces (3,005 Gm.); given a formula of 9 ounces (270 cc.) evaporated milk and 15 ounces (450 cc.) water, with barley and beef, and 1 tablespoon of "appella" and two drops of camphorated opium tincture U. S. P. every three hours.

December 3: Weight, 6 pounds 13 ounces (3,090 Gm.); 5 movements per day of more substance.

December 7: Weight, 7 pounds 4 ounces (3,289 Gm.); 3 or 4 movements per day.

December 11: Weight, 7 pounds 13 ounces (3,544 Gm.); 3 movements per day of better quality.

December 16: Weight, 8 pounds 8 ounces (3,856 Gm.); 2 or 3 movements per day of good consistency.

CASE 3.—Observations on F. F., aged 7 weeks, were as follows:

March 18, 1946: 6 watery movements yesterday; weight, 10 pounds (4,536 Gm.); given boiled whole milk, barley, beef and "appella," a level tablespoon every three hours.

March 22: Weight, 10 pounds 2 ounces (4,593 Gm.); 4 to 5 movements per day of more substance.

March 25: Weight, 10 pounds 8 ounces (4,763 Gm.); 6 firm movements per day.

April 2: Weight, 11 pounds 3 ounces (5,075 Gm.); 3 movements per day of mushy consistency.

April 8: Weight, 11 pounds 7 ounces (5,188 Gm.); 3 or 4 movements per day.
April 15: Weight, 11 pounds 12 ounces (5,330 Gm.); 2 movements per day.
April 22: Weight, 12 pounds 3 ounces (5,528 Gm.); 1 movement of good character per day.

COMMENT

The starvation treatment necessarily results in the prolonged deprivation of vital mineral and protein components of a normal diet. Such a deprivation cannot help but result in faulty tooth and bone structure, occurring as it does during this critical period of growth in infancy.

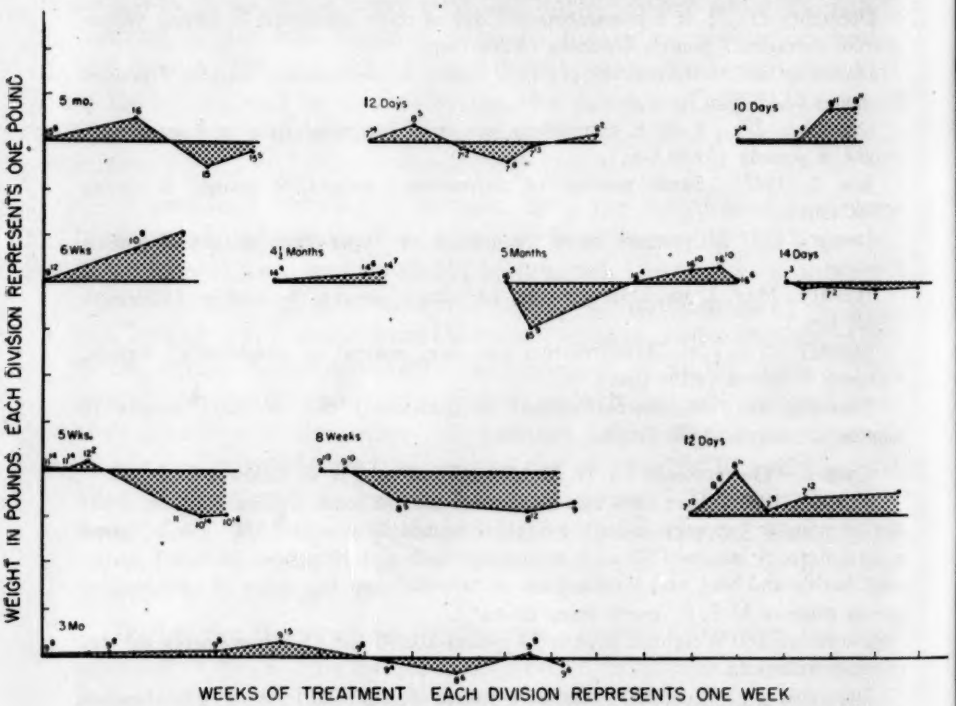

Chart 1.—Graphs showing weights of infants with diarrhea given minimal feeding, predominantly intravenously administered, not including apple powder.

Oral treatment of diarrhea in infancy has many advantages. It is a procedure which supplies all the necessary elements for normal growth. It supplies, moreover, the proteins from which antibodies may be formed to aid in the neutralization of the infectious agent. The cases can be managed in the office or outpatient department, leaving hospital personnel and hospital beds free for cases in which hospitalization is indispensable.

The uniform gains in weight and general well-being of the infants after treatment has been started is evidence that the absorption from the intestinal tract is good in spite of the diarrhea.

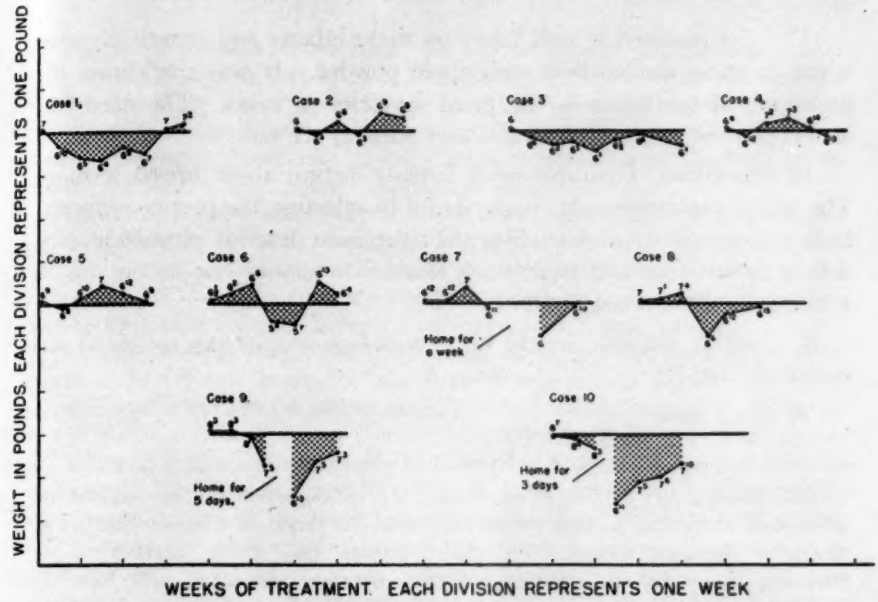

Chart 2.—Graphs of weights of infants with diarrhea given minimal feeding, predominantly orally administered, including apple powder ("appella"). Data were taken from a chart by Anderson and Nelson.

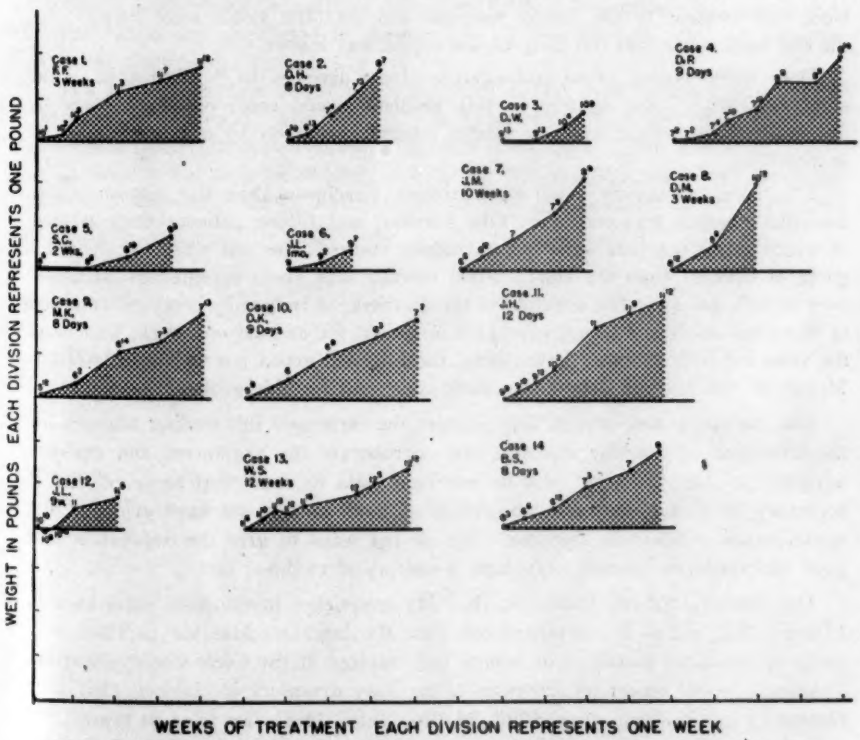
WEIGHT IN POUNDS EACH DIVISION REPRESENTS ONE POUND
Case 1. K.K. 3 Weeks
Case 2. D.H. 8 Days
Case 3. D.W.
Case 4. D.R. 9 Days
Case 5. S.C. 2 Wks.
Case 6. M.E. 1 mo.
Case 7. J.M. 10 Weeks
Case 8. D.M. 3 Weeks
Case 9. M.K. 8 Days
Case 10. O.K. 9 Days
Case 11. J.H. 12 Days
Case 12. J.L. 9 w. 11
Case 13. W.S. 12 Weeks
Case 14 B.S. 8 Days
WEEKS OF TREATMENT EACH DIVISION REPRESENTS ONE WEEK

Chart 3.—Graphs showing weights of infants with diarrhea given high calory feeding, exclusively orally administered, including apple powder ("appella").

The diet outlined is well taken by these infants and is well digested when given in conjunction with apple powder. It was used from the beginning of treatment in the great majority of cases. The needs for water, protein, fat, carbohydrates and mineral are met.

In conclusion, I paraphrase a famous dictum about breast feeding: The infant's intestine is far more skilful in selecting the proper elements, both as to quantity and quality, than the most learned physicians who debate as to what and how much should or should not be put into a solution for intravenous use.

Dr. Nina A. Anderson and Dr. W. E. Nelson gave permission for use of data from their cases.

31 Broad Street.

DISCUSSION

DR. ARTHUR W. CHUNG, New York: My colleagues and I investigated the problem of early oral feeding versus early oral starvation in infantile diarrhea by means of metabolic studies. We placed infants with severe diarrhea on the metabolic frame for the separate collection of stool and urine, and, from the chemical analysis of the food intake and the excreta, balances for minerals, fat and nitrogen were obtained.

We observed that the more food offered, the more absorbed in the presence, even, of severe diarrhea. It was true that a greater amount of the food constituents were lost incident to the higher feedings and that the stools were bulkier, but the net food going into the body of the infant was higher.

Does early feeding cause prolongation of the diarrhea to the detriment of the child clinically? The answer to this problem would seem obtainable only by observations on a large series of infants treated alternately by oral starvation and oral feeding.

I had the opportunity to go to Bratislava, Czechoslovakia, last autumn, where infantile diarrhea was endemic. One hundred and fifteen patients were treated, of which about one half were therapeutically starved; the rest were fed their full quota of calories from the start. Fluid therapy was given parenterally as necessary in both groups. The duration of the diarrhea, as judged by complete cessation of diarrheal stools and progressive gain in weight for at least one week, was about the same for both groups. If anything, the fully fed group got well a little faster. Moreover, the gain in weight was more consistent for this group.

Our metabolic and clinical data support the early and full feeding regimen for the treatment of infantile diarrhea and corroborate the arguments and evidence advanced by Dr. O'Keefe. We do not have data to show that apple powder is necessary or that it enhances absorption of food, nor do we have evidence that sugar causes relapses in diarrhea. We do not want to give the impression that good absorption is possible only with a special or modified diet.

DR. NOEL G. SHAW, Evanston, Ill.: My experience in this field dates back to 1930 to 1932, when I was associated with the late Dr. Maurice L. Blatt in a study of infectious diarrheas in infants and children at the Cook County Hospital, Chicago. In our report on 356 cases of bacillary dysentery in children (Bacillary Dysentery in Children, *Arch. Path.* **26**:216 [July] 1938), we tried to present not only details of symptoms, clinical course and bacteriologic and pathologic findings

but also our impressions of treatment. Most of the children in the groups studied were acutely ill during part of their hospitalization. The average period in the hospital for those who recovered was eleven days, which, combined with the average of four days' illness at home, made the average total illness about two weeks. However, 28 per cent of the children presented a milder form of the disease and were in the hospital less than one week.

Our experience with infectious diarrhea of the bacillary dysentery type, including the Salmonella group, made us opposed to purging and initial starvation. Such measures would have meant certain death to a number of our prostrated infants. If purging and starvation are not actually dangerous to many dysenteric children, they at least seem futile in "sweeping the bowel clean," and "putting it at rest." If one withholds fluids and food given orally until there has been no stool for twelve to twenty-four hours one may have to wait several days, during which valuable time is lost and the patient has to be maintained by parenteral administration of fluids much longer than necessary. Hypodermoclyses and venoclyses are life saving and absolutely necessary at times, but their prolonged use is to be condemned. The fact that a child's life can be sustained for long periods by intravenous alimentation, as reported by Todd and others, is highly commendable but certainly not recommended beyond the necessary period. It can actually delay recovery in acute diarrhea. There are also the dangers of incorrect amounts of parenterally administered fluids, electrolytes and proteins, as well as dangers of infection and thrombophlebitis.

Since the sulfonamide drugs have proved to be almost specific in the bacillary diarrheas except for typhoid fever, I believe succinylsulfathiazole U. S.P. ("sulfasuxidine"), sulfadiazine or, perhaps, one of the triple sulfonamide preparations used in moderation are invaluable in these cases. I use them in addition to other treatment mentioned.

In a nursery for the newborn epidemics of either virus diarrhea or bacterial diarrhea may break out. The latter may be caused by various organisms: Shigella, Salmonella or streptococci. The only safeguard is eternal vigilance and strict technic in the nursery and milk laboratory, with the prompt isolation and treatment of any baby or mother who shows diarrhea suspected of being infectious—whether viral or bacterial.

ELECTROENCEPHALOGRAPHY OF THE NEWBORN

III. Brain Potentials of Babies Born of Mothers Given "Seconal Sodium"

JAMES G. HUGHES, M.D.

BABETTE EHEMANN

AND

U. A. BROWN

MEMPHIS, TENN.

IT HAS been a common observation that babies born of mothers given heavy sedation with barbiturate drugs and other preparations may themselves show oversedation, even to the point of severe respiratory depression. The relation of oversedation of mothers to the neonatal death rate has been commented on by numerous investigators. The stress has been placed on severe oversedation, and little has been said of that large group of infants who are born with milder degrees of drowsiness.

It is the purpose of this paper to present electroencephalographic observations on a group of newborn infants whose mothers were given varying doses of "seconal sodium" (sodium 5-allyl-5-[1-methyl-butyl] barbiturate) during labor. The technic used for obtaining electroencephalograms on neonates was described in another communication.[1] All the data presented were obtained on full term, normal infants born of women whose labors and deliveries were uneventful.

The chief observation in this investigation was a striking depression in cortical electrical activity noted to a greater extent in the bipolar runs than in the monopolar tracings. Figure 2 in the previous paper[1] and figure 1 show the decided contrast in tracings obtained from infants whose mothers received no sedative drug as compared with those from newborn infants whose mothers were given a barbiturate preparation. A total of 51 electroencephalograms were obtained on 20 of these infants, tracings on 11 of whom were made during the first twenty-four hours of life.

From the Division of Pediatrics, University of Tennessee College of Medicine.

This work was supported by a grant from the United States Public Health Service.

1. Hughes, J. G.; Ehemann, B., and Brown, U. A.: Electroencephalography of the Newborn: I. Studies on Normal Full Term Sleeping Infants, Am. J. Dis. Child. **76**:503 (Nov.) 1948.

Graphs of curves for percentage frequencies were made from the electroencephalograms obtained in the first twenty-four hours, and the mean curve was superimposed on graphs of percentage frequency curves constructed from tracings on a larger series of normal, full term infants whose mothers had received no sedation (figs. 2 to 6). While this quantitative method of presenting the electroencephalographic observations is less informative than a glance at the sample tracings themselves, it does give expression to the fact that waves of slow frequency, which in the newborn infant whose mother received no sedation are usually of a higher amplitude, are greatly decreased. If curves for

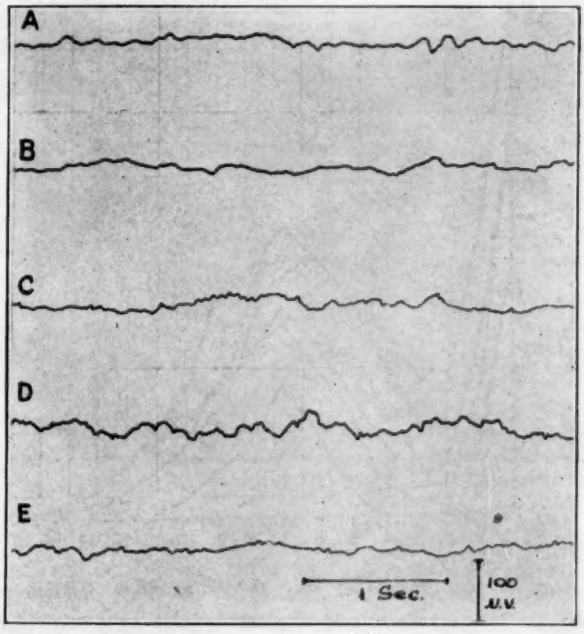

Fig. 1.—Five electroencephalographic tracings of normal, full term, sleeping infants whose mothers were given sedation with "seconal sodium": *A* is the right frontal monopolar tracing of a child 52 hours old; *B* is the right precentral monopolar tracing of a child 26 hours old; *C* is the left occipital monopolar tracing of a child 1½ hours old; *D* is the right frontal to right precentral bipolar tracing of a child 2 days old, and *E* is the left precentral to the left occipital bipolar tracing of a child 28 hours old.

standard deviation for the series in which "seconal sodium" was given had been superimposed also on the graphs of percentage curves of the series in which no sedative was given, this fact would be more obvious. While slow waves of moderate amplitude were conspicuously decreased in the tracings for the series given "seconal sodium," fast waves of low amplitude were increased, so that the mean percentage frequency curve for the "seconal sodium" series exceeded the mean for the babies

whose mothers were given no sedation in the right side of the graphs where the fast waves are plotted.

All 11 infants on whom electroencephalograms were obtained in the first twenty-four hours showed noticeable drowsiness and some of them were quite sluggish. Of the infants whose tracings were taken on the second day of life, some were still a bit drowsy, while most of them were as alert as normal. In the group whose tracings were made on the third day of life, the infants were all normally alert.

Electroencephalograms obtained on the first day showed uniform cortical electrical depression; those obtained on the second day showed

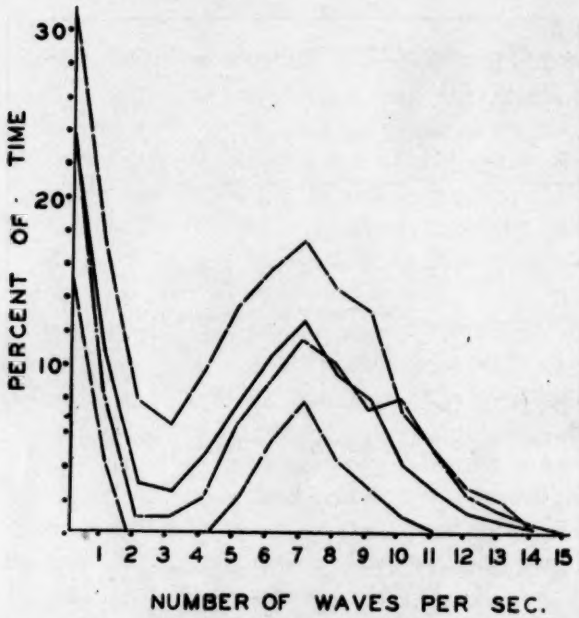

Fig. 2.—Graph of frequency curves of 10 frontal monoplar tracings during the first twenty-four hours after birth on babies whose mothers were given sedation with "seconal sodium." The mean curve for these infants, indicated by the irregularly broken line, was superimposed on the solid line indicating the mean and on the regularly broken line indicating the standard deviation of frequencies for normal, full term, sleeping infants whose mothers received no sedative or analgesic drug during labor.

the same pattern no matter whether the baby was alert or drowsy, and those taken on the third day showed a tendency to return to the normal pattern. Thus, although several of the babies had overcome their drowsiness by the second day, their electroencephalograms were still abnormal, and the abnormalities persisted into the third day in certain of the infants who had serial studies from the first day on. It is apparent, therefore, that the electroencephalogram detects a stage of electrical depression in some infants at a time no clinical drowsiness exists.

It did not seem to make any difference whether the tracings on the babies showing sedation from "seconal sodium" were taken while they were awake or while they were asleep. In infants asleep or awake the same conspicuous decrease was apparent in slow waves of moderate amplitude.

Not enough infants were studied to warrant any statement as yet concerning the electroencephalographic effects of varying total dosage of "seconal sodium" and timing of doses in relation to delivery.

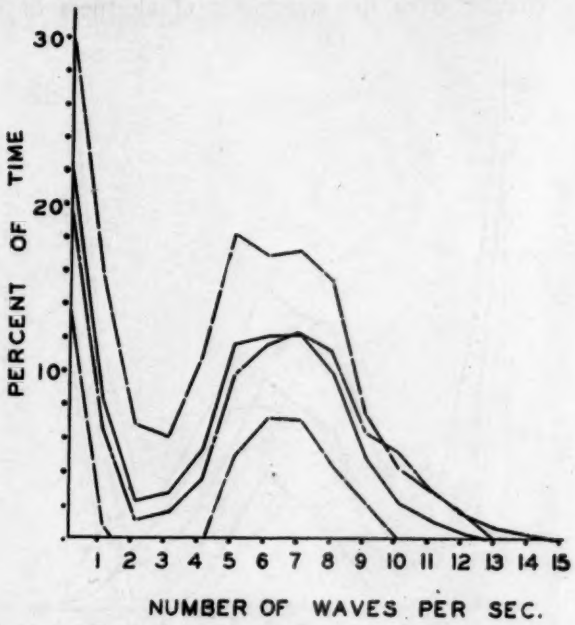

Fig. 3.—Graph of frequency curves of 10 precentral monopolar tracings during the first twenty-four hours after birth on babies whose mothers were given sedation with "seconal sodium." The mean curve for these infants, indicated by the irregularly broken line, was superimposed on the solid line indicating the mean and on the regularly broken lines indicating the standard deviations for normal, full term, sleeping infants whose mothers were given no sedative or analgesic drug during labor.

COMMENT

The observations presented show that the electroencephalogram is a sensitive indicator of cortical electrical depression produced by sedation with "seconal sodium." The extremely low amplitudes of the brain waves of infants born of mothers under sedation from "seconal sodium" is in distinct contrast to the normal electroencephalographic patterns of newborn infants whose mothers were given no sedative agent during labor, or who were delivered with the use of caudal

analgesia.[1] Evidence of the sensitivity of electroencephalography in detecting cortical depression lies in the fact that waves of low amplitude were found in some infants who did not appear clinically drowsy. One may speak of clinical and subclinical cortical depression, if by the latter term is meant electrical depression without clinical drowsiness.

It is apparent how this method of study could be applied to the evaluation of dosages of various sedative and analgesic agents given to the mother in regard to their effect on the baby's brain waves and on his clinical behavior from the standpoint of alertness or drowsiness.

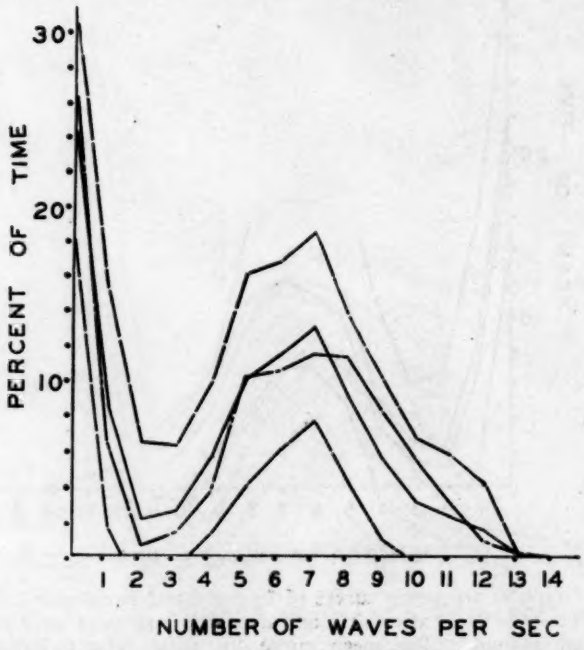

Fig. 4.—Graph of frequency curves of 9 occipital monopolar tracings during the first twenty-four hours after birth on babies whose mothers were given sedation with "seconal sodium." The mean curve for these infants, indicated by the irregularly broken line, was superimposed on the solid line indicating the mean and on the regularly broken lines indicating the standard deviations for normal, full term, sleeping infants whose mothers were given no sedative or analgesic drug during labor.

Naturally, the ideal doses of the agents would be those which gave the mother the proper degree of comfort yet spared the baby the peril of oversedation. It is problematic whether any such ideal can be achieved, in view of the fact that when the mother is under sedation the baby within her uterus is bound to receive some of the agent through the fetal circulation. It is more probable that a great deal may be learned about avoidance of excessive doses of the drugs by obtaining a

sharper definition of what the baby's brain will stand without the occurrence of clinically significant depression.

Our group of infants is much too small to permit any sweeping conclusions, but the study does indicate the possibility of utilizing the method to advantage in further investigations. Many different agents need evaluation, both in regard to total dosage administered during labor and in timing of doses prior to delivery. A much larger group of infants needs to be studied by the technic, and these studies require detailed clinical and laboratory data to determine the extent to which clinical significance can be attributed to electroencephalographic abnor-

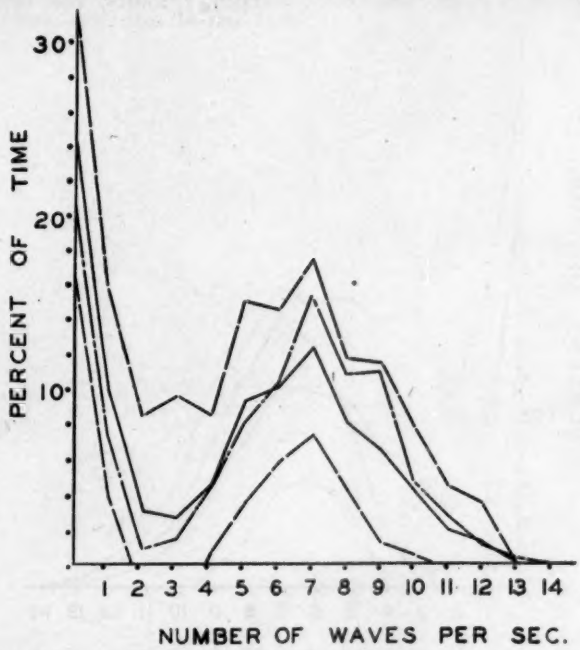

Fig. 5.—Graph of frequency curves of 10 frontal-precentral bipolar tracings during the first twenty-four hours after birth on babies whose mothers were given sedation with "seconal sodium." The mean curve for these infants, indicated by the irregularly broken line, was superimposed on the solid line indicating the mean and on the regularly broken lines indicating the standard deviations for normal, full term, sleeping infants whose mothers were given no sedative or analgesic drug during labor.

malities. For example, correlation of the electroencephalographic findings with speed of expansion of the lungs and the relation of cortical electrical depression of varying degrees to the incidence of persistent atelectasis might be of practical value. Applications of the method in other ways come to mind.

In brief, electroencephalography of the newborn offers a new approach to a better understanding of a most critical episode—the

business of being born. It must be interpreted against a kaleidoscopic background of complex physiologic adjustments and intricate interplay of factors which may produce pathologic changes.

SUMMARY AND CONCLUSIONS

On a series of 20 newborn infants whose mothers had been given "seconal sodium" during labor, 51 electroencephalograms were obtained. Of these infants, 11 were subjected to electroencephalography on the first day of life, some of them within the first few hours.

In comparison to electroencephalographic patterns previously found characteristic of normal, full term, sleeping infants, the brain waves

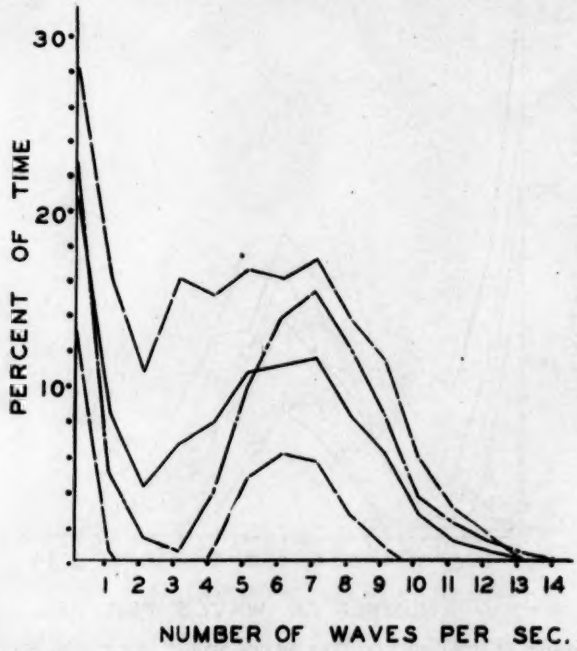

Fig. 6.—Graph of frequency curves of 9 precentral-occipital bipolar tracings during the first twenty-four hours after birth on babies whose mothers were given sedation with "seconal sodium." The mean curve for these infants, indicated by the irregularly broken line, was superimposed on the solid line indicating the mean and on the regularly broken lines indicating the standard deviations for normal, full term, sleeping infants whose mothers were given no sedative or analgesic drug during labor.

of these babies showed a striking electrical cortical depression characterized by a pronounced decrease in slow waves of moderate amplitude and some increase in fast waves of low amplitude.

The apparent effect of "seconal sodium" in depressing the electrical activity of the baby's cortex persisted for three days in some infants, even when clinical signs of drowsiness had been overcome. This

indicates that electroencephalography is a more sensitive index of cortical depression than mere clinical observation.

The use of electroencephalography of the newborn is suggested as a technic with which to explore to a greater degree dosages of sedative and analgesic agents given to the mother in regard to their effects on the brain waves of the baby.

20 South Dunlap Street (3).

Dr. T. S. Hill, professor of psychiatry, University of Tennessee College of Medicine, and director, Gailor Psychiatric Hospital, and Dr. Hudson Jost, assistant professor of psychiatry and director, Psychophysiological Laboratories, Gailor Psychiatric Hospital, assisted in this study.

ELECTROENCEPHALOGRAPHY OF THE NEWBORN

IV. Abnormal Electroencephalograms of the Neonate

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BABETTE EHEMANN

AND

U. A. BROWN

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WHILE the subject of electroencephalography in children and adults has received extensive consideration by many observers, no studies have been published on abnormal electroencephalograms obtained on infants in the first days of life. Yet the matter of being born is such a physiologic adventure and the hazards to the brain so obvious that one would expect to find evidence of cortical electrical abnormality in those newcomers who have not survived too well the physical and chemical stresses incident to labor and delivery.

It is the purpose of this communication to present data on a group of 8 full term newborn infants whose electroencephalograms showed definite abnormalities. Seven of these infants had clearcut evidence of neurologic disorder at the time the tracings were taken. One showed no unusual clinical symptoms or signs in the nursery, but his electroencephalograms were observed to be abnormal. It will require a considerably larger number of cases and a far greater number of serial electroencephalograms and clinical observations to establish fully the prognostic import of electroencephalographic abnormalities encountered in the neonate. Furthermore, a large series of newborn infants showing electroencephalographic abnormalities will have to be followed to autopsy in order to give a more definite correlation between organic damage to the brain and localization of abnormal electroencephalographic findings.

Our studies on abnormal electroencephalograms in the neonate were carried out in conjunction with the primary project of determining the normal electroencephalographic patterns in the newborn, and our series of abnormal cases is small. Still, they represent the only group so far known to be so studied, and the findings and the follow-up observations are of such interest that they are presented in this preliminary

From the Division of Pediatrics, University of Tennessee College of Medicine.

This work was supported by a grant from the United States Public Health Service.

report. The interpretation of these abnormal tracings was considered against the background of a large group of normal, full term newborn infants whose electroencephalographic patterns are reported in another communication.[1] In that report the technic employed in obtaining electroencephalograms in the neonate was presented, and an evaluation or normal patterns was made. Sample normal tracings are shown in figure 2 of a previous paper.[1]

The present paper concerns data on 8 full term newborn infants less than 6 days of age.

REPORT OF CASES

A. CASES WITH NEUROLOGIC SYMPTOMS AND ABNORMAL ELECTROENCEPHALOGRAMS

CASE 1 *(Baby H.).—Clinical Features.*—This full term infant was delivered of a primiparous mother with the use of caudal analgesia with episiotomy and low forceps. The labor had been prolonged and hard because of cephalopelvic dispro-

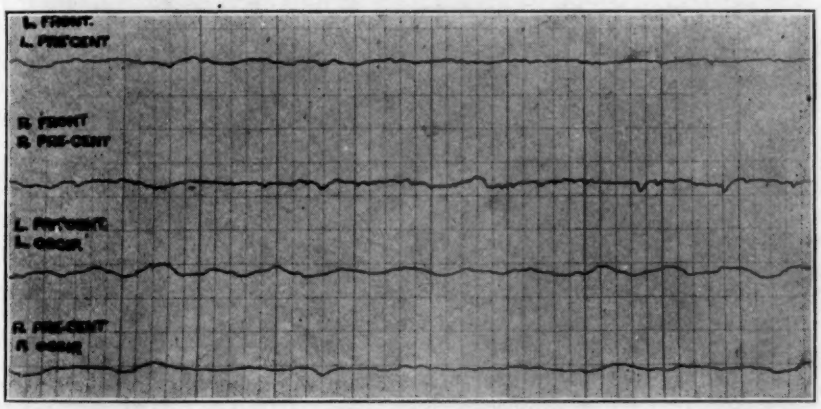

Fig. 1 (case 1).—Electroencephalogram taken twenty-four hours after birth on an infant with widespread subarachnoid hemorrhage over both surfaces of the cerebral cortex, proved at autopsy. Note lack of amplitude in the bipolar tracings. The same straight line picture was seen in the monopolar runs.

portion. The presentation of the fetus was right occipitotransverse. The child was in critical condition immediately after birth and was resuscitated with use of a tracheal catheter, oxygen, alpha-lobeline and nikethamide N.N.R. There was cyanosis and a feeble cry. Within twenty-four hours of birth the anterior fontanel was noted to be bulging; there was a cephalic type cry; opisthotonos developed, and hemorrhage into the anterior chamber of the right eye, with dilatation of the pupil, was noted. Great difficulty in breathing occurred almost from birth, with rapid grunting respirations and much bloody mucus in the air passages. The conjunctivas of both eyes were greatly congested. Suprasternal and subcostal retraction occurred on inspiration, and loud, moist generalized rales were heard throughout both pul-

1. Hughes, J. G.; Ehemann, B., and Brown, U. A.: Electroencephalography of the Newborn: I. Studies on Normal, Full Term, Sleeping Infants, Am. J. Dis. Child. **76**:503 (Nov.) 1948.

monary fields. The bones at the right parietal eminence were overriding. Death occurred forty hours after birth.

Electroencephalographic Features.—When the child was twenty-four hours old an electroencephalogram was obtained at the height of the aforementioned symptoms. The run was made for a two minute period during which oxygen was not given. The electroencephalogram (fig. 1) showed notable suppression of cortical electrical activity over all areas on both sides of the brain. Frontal, precentral and occipital leads were obtained. In all leads, both monopolar and bipolar, the tracings appeared as almost straight lines, with infrequent random waves of extremely low amplitude. Fast activity was seen in only the right frontal-precentral bipolar lead. The usual fast frequencies of low amplitude seen in our studies on normal newborn infants of this age were absent; also absent were the short bursts of alpha and delta activity encountered in the normal group. The most striking observation was extremely low amplitude in all leads.

Clinical Diagnosis.—In view of the clinical and electroencephalographic features of the case, it was considered that the child had extensive cerebral hemorrhage, with

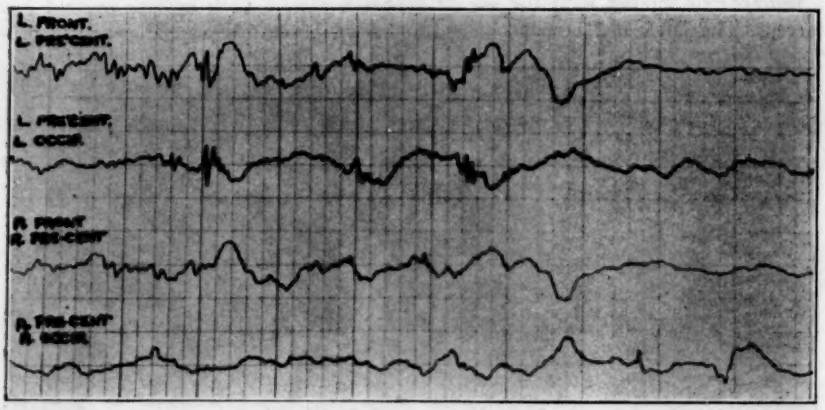

Fig. 2 (case 2).—Electroencephalogram taken sixteen hours after birth and five hours prior to onset of convulsions. Note phase reversals in the left frontal-precentral and left precentral-occipital tracings, indicating localization of cortical abnormality in the left precentral area.

widespread distribution over both sides of the cortex. Atelectasis and pneumonia were thought to be present on the basis of severe obstruction of the respiratory tract with bloody mucus. The chief cause of death was thought to be cerebral anoxia incident to hemorrhage of the brain and deficient oxygenation caused by the aforementioned respiratory factors.

Autopsy Observations.—Postmortem examination revealed widespread subarachnoid hemorrhages over both sides of the cortex, with extreme congestion of cortical vessels. Both lungs showed a hemorrhagic type of pneumonia with heavy congestion of vessels, and there was hemorrhage into the interstitial tissue and alveoli. The alveoli contained fibrin, mononuclear cells, lymphocytes and some polymorphonuclear leukocytes. There were many atelectatic areas and areas of compensatory emphysema. Hemorrhagic areas under the pleura were also seen.

Case 2 *(Baby J.).—Clinical Features.*—This full term infant was delivered of a primiparous mother from a left occipitoanterior presentation after an uneventful thirty-six hours of labor. No forceps were used. The infant had delayed respiration

and was resuscitated by clearing the respiratory passages and giving oxygen. The cry was delayed and feeble, and the child was cyanotic when brought to the nursery. After seven hours of continuous administration of oxygen, the cyanosis cleared completely and the cry was strong. In spite of constant administration of oxygen periods of cyanosis recurred; the cry became feeble, the child seemed listless, and little interest was shown in feedings. Generalized convulsive movements started twenty-one hours after birth, the repeated seizures lasting slightly less than one minute. Under sedation with phenobarbital sodium and with the administration of oxygen and other supportive measures, the child continued having generalized convulsions for forty-eight hours. After the severe convulsions had ceased, tremors of all extremities were noted until 9 days of age, at which time the infant was discharged home to be followed in the clinic.

Electroencephalographic Features.—The first electroencephalogram was taken when the child was sixteen hours old, before any convulsive movements had been noted clinically (fig. 2). In the monopolar frontal, precentral and occipital leads from both sides of the brain, and in frontal-precentral and precentral-occipital bipolar leads from both sides, were noted bursts of high frequency, high amplitude

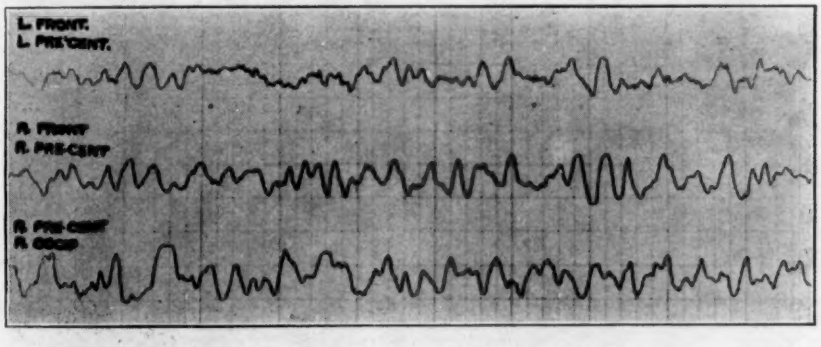

Fig. 3 (case 2).—Electroencephalogram taken at 7 months of age, showing prominent dysrhythmia.

waves and spikes. These were much more prominent in monopolar and bipolar leads from the frontal and precentral areas bilaterally. Evidences of phase reversal were noted, particularly in the left frontal-precentral and precentral-occipital bipolar leads, indicating localization of pathologic changes in the precentral area on the left. Phase reversals were also noted on the right side to a less extent, indicating localization of damage in the right precentral area also, but probably to a less degree than in the left precentral area. When the baby was 40 hours old, the second electroencephalogram was obtained. It confirmed the observations on the first tracings, with particular prominence of localization of damage to the left precentral area.

Follow-Up Study.—The baby was under observation for seven months, during which time he was normal clinically, but still abnormal from the standpoint of electroencephalographic findings. An electroencephalogram obtained at this age (fig. 3) showed pronounced dysrhythmia from all leads on both sides of the brain. There were frequent bursts of fast activity which commenced simultaneously on the left and on the right in the frontal-precentral areas. Also on both sides, but with shorter bursts and less amplitude, the same findings were noted in the precentral-occipital bipolar leads. Both monopolar precentral leads showed striking dysrhythmia and bursts of high frequency waves.

CASE 3 *(Baby F.).—Clinical Features.*—This full term infant was delivered of a primiparous mother by cesarean section. The reason for the section was cephalopelvic disproportion which prevented the head from being engaged after a suitable observation of hard labor of only a few hours' duration. No sedative or analgesic drug was given to the mother for thirteen hours prior to the section, which was done under continuous caudal analgesia. The baby was delivered uneventfully; respiration was delayed slightly, but the child was easily resuscitated with the use of a tracheal catheter and oxygen and appeared to be normal when sent from the delivery room to the nursery. However, cyanosis was noted immediately afterward in the nursery, and a nonpersistent strabismus was present. After the first few hours, in which slight cyanosis was noticed in spite of administration of oxygen, the infant was considered to be normal.

Electroencephalographic Features.—An electroencephalogram was obtained when the infant was 37 hours old (fig 4). The most striking observation was almost complete suppression of cortical electrical activity, as evidenced by practically complete absence of amplitude, the tracings appearing as straight lines. The electrodes

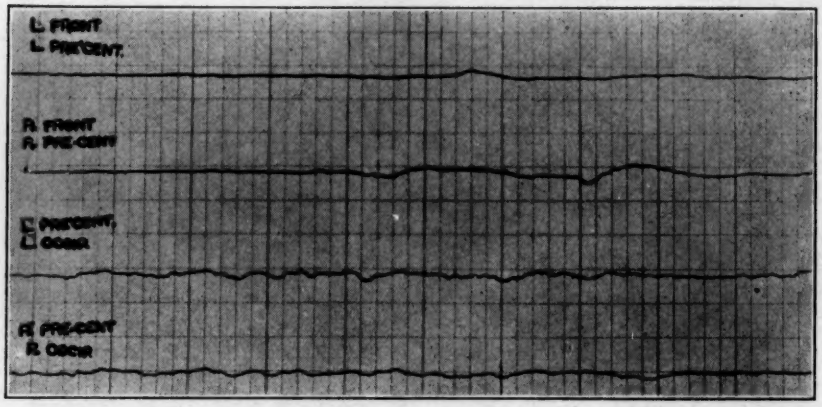

Fig. 4 (case 3).—Electroencephalogram taken thirty-seven hours after birth, showing widespread cortical electrical depression.

and pens were checked, but the lack of amplitude persisted over and over again in different sections of the total run, particularly in the frontal-precentral leads bilaterally. By an increase in the amplification of the machine it was possible to obtain bipolar tracings from the left and right precentral-occipital leads which showed a slight increase in height of waves, but suppression of amplitude was still noted in the frontal-precentral bipolar leads.

Electroencephalograms were obtained every day for eight days. From the second day on, a steady increase in cortical electrical activity was noted, but the tracings still did not become normal. Even on the eighth day suppression of amplitude was noted in bipolar tracings taken from the left side of the head, that is, the left frontal-precentral and precentral-occipital leads. On the sixth day, the electroencephalogram (fig. 5) showed multiple fast spike activity of low amplitude in the left precentral-occipital bipolar lead. There was no spiking in the left frontal-precentral bipolar lead. However, in a subsequent section of the run, high isolated single spikes were noted in both the left and the right frontal-precentral bipolar leads.

Follow-Up Study.—The child was followed to the age of 6 months and seemed normal in all respects except for one generalized convulsion which occurred at 5

months of age when he had an acute febrile disturbance. The electroencephalogram still showed decided abnormalities persisting to the age of 6 months. High amplitude random spikes were noted frequently in the left and right frontal-precentral bipolar leads. Dysrhythmia was found in all leads, the waves varying in frequency and amplitude, with no semblance of an orderly pattern.

CASE 4 *(Baby J.).—Clinical Features.*—This full term newborn infant was delivered of a primiparous mother from a right occipitoanterior presentation with high forceps, the mother having been given caudal analgesia. The mother had a contracted pelvis and there was considerable cephalopelvic disproportion. No resuscitation was required, and the cry and color were good. On the following day, twenty-two hours after birth, convulsive movements of the face and all extremities developed, more on the right than on the left. Rotatory nystagmus also occurred. The neck was limp. After the convulsive movements ceased, mild generalized spasticity was noted. The child was placed in an oxygen tent and sedative drugs were administered. In three days the repeated convulsions had ceased, and she was discharged home in good condition on the tenth day, but with a guarded prognosis.

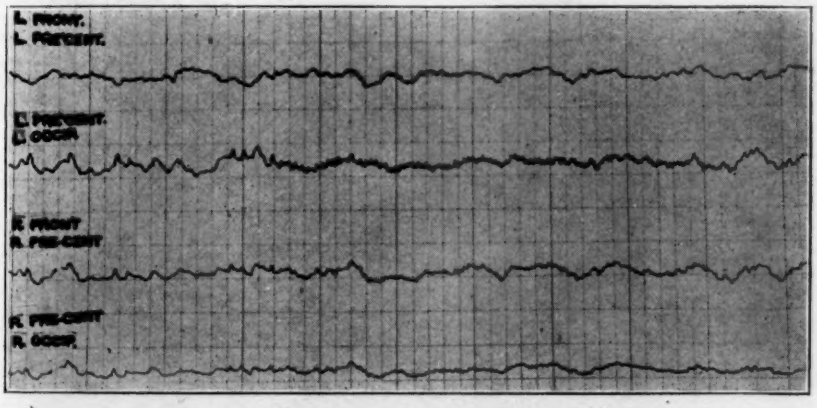

Fig. 5 (case 3).—Electroencephalogram taken at 6 days of age, showing multiple spike activity in the left precentral-occipital bipolar tracing.

Electroencephalographic Features.—The electroencephalogram (fig. 6) obtained during the convulsions when the child was twenty-four hours old showed gross dysrhythmia in all leads. Fast frequencies at low amplitudes were noted on the left side in the monopolar runs to a greater extent than on the right, and bipolar runs showed more fast activity on the left than on the right. Although all four extremities were twitching, those on the right side of the body were convulsing to a greater extent than those on the left, a probable correlation with the fact that the electroencephalographic abnormalities were more pronounced in tracings from the left side of the brain than from the right. During the convulsions there were continuous paroxysmal bursts of waves showing high amplitude, but varying in degree in the neighborhood of 100 microvolts, appearing simultaneously over the left and right frontal-precentral areas of the brain. The sharp waves observed in the right frontal-precentral lead are not to be confused with electrocardiographic activity because of the character of the waves during the convulsive episode.

Follow-Up Study.—Tracings obtained three weeks later showed great improvement in the electroencephalographic findings, but they were still abnormal in the frontal-precentral leads on both sides. The abnormalities consisted in sharp single

random spikes and fast frequencies of varying high amplitude, but the amplitude was not as great as in the initial tracings. During follow-up study over eight months clinical abnormalities did not occur. Unfortunately, it was impossible to obtain a reliable electroencephalogram at this time, owing to difficulty in keeping the infant still during the runs.

CASE 5 *(Baby D.).—Clinical Features.*—This full term infant was delivered of a jaundiced primiparous mother from a right occipitoanterior presentation with episiotomy and low forceps. The mother was given caudal analgesia. The cause of the jaundice was thought to be a gallstone in the common duct. The labor was thirteen hours long, and the condition of the mother was good. The infant breathed spontaneously and required no resuscitative efforts. The child had atresia of the anus, which was subsequently operated on with the area under local anesthesia. Convulsive movements of the right side of the body were noted at 14 days of age, the movements lasting about four minutes with each convulsion, followed by periods of rigidity for five minutes. There was strabismus during the convulsions. Similar convulsions were noted on the left side the following day. Repeated gen-

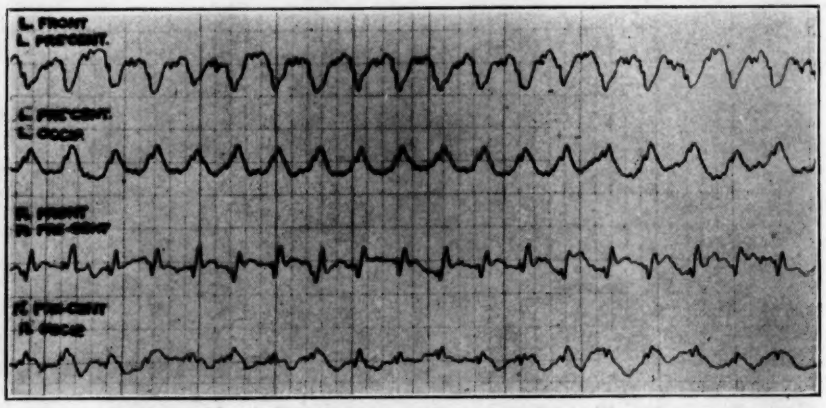

Fig. 6 (case 4).—Electroencephalogram taken twenty-four hours after birth on an infant during generalized convulsions, showing abnormalities in all tracings.

eralized severe convulsions were present for the next three days, after which they ceased. Phenobarbital, oxygen and supportive measures were employed. The baby was discharged at 21 days of age, having showed no neurologic abnormalities for the previous three days.

Electroencephalographic Features.—An electroencephalogram was obtained on the infant when he was 16 days old, two days after the convulsions had started (fig. 7). During the course of the run, subclinical and clinical seizures were noted. As the run started there was little abnormality. Suddenly, bursts of high frequency, high amplitude spikes occurred simultaneously from both frontal and both precentral monopolar leads. The episode lasted approximately thirteen seconds, and the infant made no movement during this subclinical seizure. At the end of thirteen seconds of electroencephalographic abnormalities, the child began a generalized convulsion, and a sharp increase in frequency occurred in the right and left frontal monopolar leads, but also to a less extent in the left and right precentral monopolar leads. Similar observations were encountered in the left frontal-precentral bipolar lead. The spiking activity shown in figure 8 is not due to electrocardiographic

activity because of extremely high frequency in the first part of the tracing, variability in amplitude, inconsistency in contours and the building up in both frequency and amplitude during the convulsion.

Follow-Up Study.—The child was followed in the clinic for six months, during which time his course appeared normal as far as the nervous system was concerned, although the anal stenosis offered therapeutic difficulties. The mother refused to permit subsequent electroencephalographic studies, so that we are unable to report the present status of the brain waves.

CASE 6 *(Baby S.).—Clinical Features.*—This full term infant was delivered of a woman who in two previous pregnancies had had convulsions at the time of labor and delivery and whose condition in this particular pregnancy was diagnosed as mild toxemia. She became disoriented during labor but had no convulsions. Over a nine hour period, terminating six hours before birth of the baby, she was given a total of 7½ grains (0.48 Gm.) of "seconal sodium" and 200 mg. of meperidine hydrochloride N.N.R. ("demerol"). The presentation was right occipitoanterior. During the delivery, which was spontaneous without administration of any other

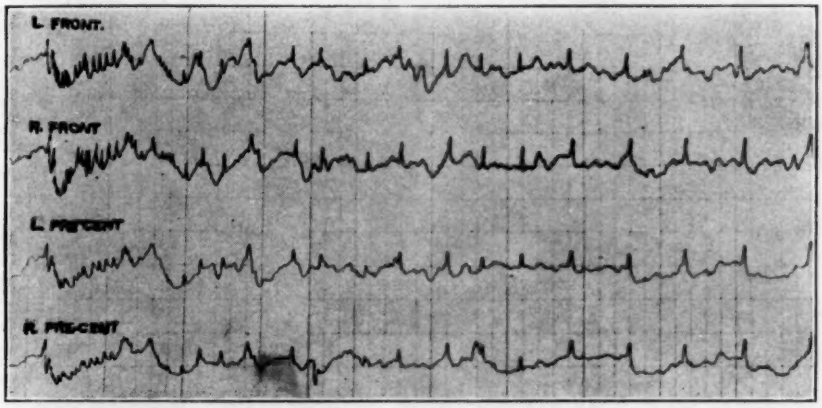

Fig. 7 (case 5).—Electroencephalogram taken at 16 days of age, showing beginning of generalized convulsion at time of tracing.

sedation or anesthesia and without use of forceps, considerable difficulty was encountered in delivering the shoulders. The cord was wrapped tightly about the baby's neck and had to be cut before the shoulders could be delivered. Respiration was delayed, and the baby did not breathe spontaneously. It was difficult to resuscitate the child. When admitted immediately to the nursery, he was cyanotic and all extremities were spastic. Slight intermittent tremors of all extremities were present for the first day. There was considerable difficulty in maintaining respiration, in spite of oxygen and supportive measures. After three hours the respiration improved but was still rapid and abdominal in type. The arms and neck were stiff. The cry was shrill and high pitched. Opisthotonos was present from the start. After forty-eight hours the child had made great improvement, although the neck was still somewhat stiff. No convulsions were noted at any time. At nine days of age he was discharged home to be followed in the clinic.

Electroencephalographic Features.—An electroencephalogram (fig. 8) was obtained when the infant was 24 hours old and quite abnormal neurologically, as indicated previously. However, the baby did not twitch during the electroencephalo-

graphic run but was very still. The electroencephalogram differed decidedly from what we found to be the usual electroencephalographic pattern in infants whose mothers were given 6 grains (0.39 Gm.) or more of "seconal sodium."[2] The chief difference was that the waves in all leads were of high amplitude. Each lead showed prominent dysrhythmia, but it was not simultaneous in the various leads. There were no localizing indications, but rather evidence of generalized cortical abnormality.

Follow-Up Study.—The mother refused to bring the child back for subsequent clinical and electroencephalographic observations, in spite of repeated efforts to follow the case. Although she did not permit the child to be examined again, she did say that he had seemed completely normal for six months.

CASE 7 *(Baby C.).—Clinical Features.*—This full term infant was the second child of a 16 year old mother who had been in labor eighteen hours prior to delivery with the use of caudal analgesia. The child was delivered with episiotomy and low forceps, the presentation being converted from left occipitoposterior to left occipitoanterior. The observations on maternal blood pressure during continuous caudal

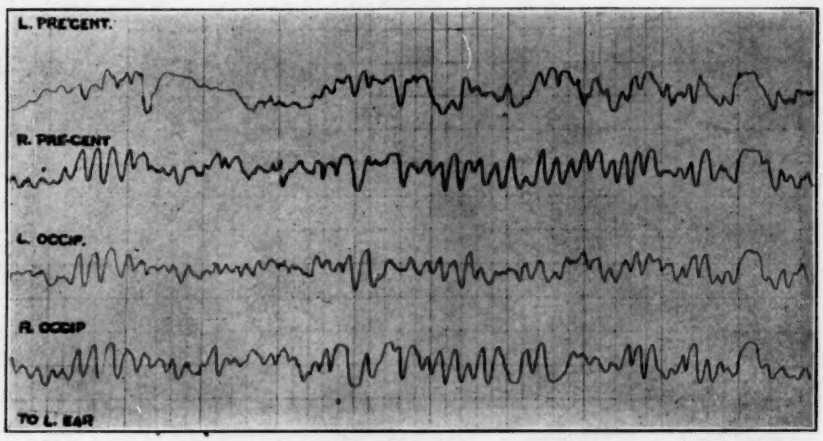

Fig. 8 (case 6).—Electroencephalogram taken at twenty-four hours after birth, showing pronounced dysrhythmia and high amplitude in all tracings.

analgesia are of interest since the sudden hypotension with low pulse pressure which developed may have caused cerebral anoxia in the infant, in spite of the fact that administration of oxygen was promptly started when the pressure fell. Caudal analgesia was started at 8:45 p.m. when the mother's blood pressure was 154 systolic and 98 mm. of mercury diastolic; at 9:20 p.m. it was 168 systolic and 110 diastolic. Then it began falling rapidly, to reach a low level of 82 systolic and 70 diastolic at 9:45 p.m. For a period of ten minutes the mother's systolic pressure was between 82 to 100 mm. and the diastolic pressure was 70 mm. of mercury. During a part of this period the systolic pressure of the mother was well below 90 mm. At 9:45 p.m. ephedrine was given to the mother, and the blood pressure began climbing to normal levels. The baby appeared normal at birth, needed no resuscitation and had

2. Hughes, J. G.; Ehemann, B., and Brown, U. A.: Electroencephalography of the Newborn: III. Brain Potentials of Babies Born of Mothers Given "Seconal Sodium," Am. J. Dis. Child., this issue, p. 626.

an uneventful course in the nursery until 4 days of age, at which time the left side of the body had definite tremors, which lasted thirty seconds. It was the clinical opinion that damage had probably occurred to the right side of the brain. The child was taken from the nursery without medical approval.

Electroencephalographic Features.—When the baby was 40 hours old the first electroencephalogram (fig. 9) was taken, two days before any clinical abnormality was noted. Phase reversals were noted in the right frontal-precentral and right

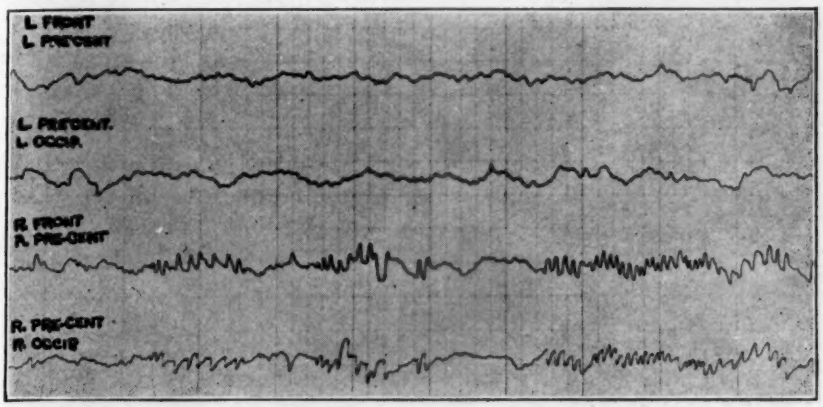

Fig. 9 (case 7).—Electroencephalogram taken forty hours after birth, two days before tremors developed on left side of body. Note phase reversals in the right frontal-precentral and right precentral-occipital tracings, indicating localization of cortical abnormality in the right precentral area.

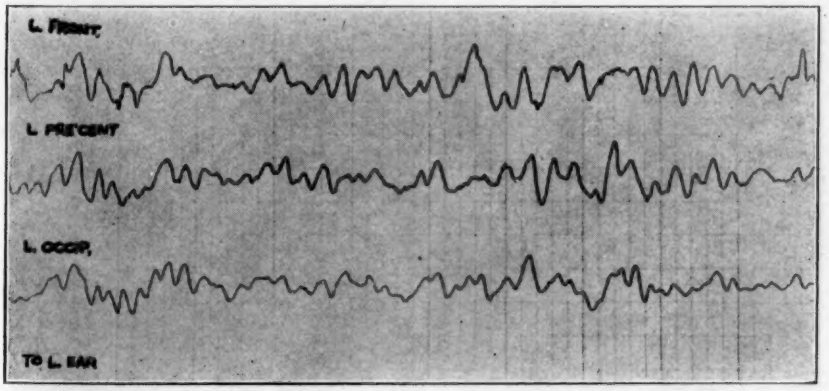

Fig. 10 (case 7).—Electroencephalogram taken at 6 months of age, showing total dysrhythmia in all the tracings.

precentral-occipital leads, indicating focal cortical damage in the right precentral area. It is interesting that this electroencephalographic evidence of abnormality on the right side of the brain was found two days before tremors developed on the left side of the body. In addition to phase reversals, the same aforementioned bipolar leads showed sharp waves of moderate amplitude. The rest of the leads showed no abnormality.

Follow-Up Study.—The child was normal clinically for a follow-up period of six months. At this time, however, the electroencephalogram showed total dysrhythmia in all the monopolar and bipolar leads, indicating probable widespread cortical abnormality (fig. 10).

B. CASE WITH NO NEUROLOGIC SYMPTOMS BUT WITH ABNORMAL ELECTROENCEPHALOGRAMS

CASE 8 *(Baby S.).—Clinical Features.*—This full term infant, weighing 6 pounds 10½ ounces (3,019 Gm.), was the second of twins, being born fifteen minutes after

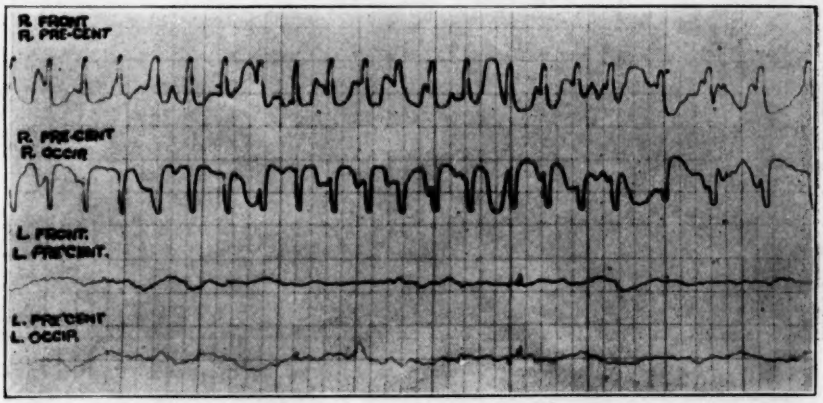

Fig. 11 (case 8).—Electroencephalogram taken at 6 days of age, showing phase reversals in the right frontal-precentral and right precentral-occipital tracings, indicating localization of cortical abnormality in the right precentral area.

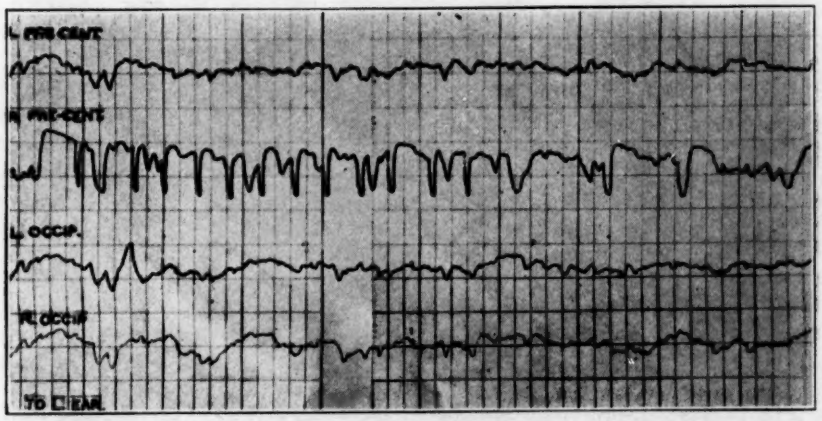

Fig. 12 (case 8).—Electroencephalogram taken at 6 days of age showing episodes of high amplitude square waves with irregularly indented tops.

the first. The labor lasted four hours. This was the mother's second pregnancy. The mother was given 4½ grains (0.29 Gm.) of "seconal sodium" over a two hour period ending one and one-half hours before the delivery of the infant. The baby had a shoulder presentation and was delivered by version and breech extraction. No resuscitation was required, and the baby was considered to be normal. There

followed an uneventful five days in the nursery, after which the child was discharged home in good condition.

Electroencephalographic Features.—Electroencephalograms obtained one hour after birth, on the second day and on the third day were all considered to be normal. In the electroencephalogram obtained on the fourth day, the first indications of abnormality occurred. There were occasional evidences of phase reversals in the right frontal-precentral and precentral-occipital leads, but this was not sustained or clearcut, since the reversals were so isolated and of such low amplitude. On the fifth day the left precentral-occipital bipolar run showed frequent isolated sharp spikes ranging from 20 to 70 microvolts in amplitude. The right frontal-precentral and preoccipital leads showed definite suppression of electrical activity throughout the entire run. On the sixth day the electroencephalogram (fig. 11) showed clearcut evidence of phase reversals in the right frontal-precentral and right precentral-occipital leads, indicating focal cortical abnormality in the right precentral area. These phase reversals were sustained throughout the total run of two minutes. Bipolar tracings from the left side of the head showed no abnormality. All the monopolar runs from the left side of the head were normal, as were the frontal and occipital monopolar runs on the right. However, the right precentral monopolar run showed serious abnormality, consisting in an episode of high amplitude square waves with irregularly indented tops (fig. 12). The episode lasted about five seconds.

Follow-Up Study.—Three months later the electroencephalogram still showed abnormal signs, consisting in definite phase reversals in the right frontal-precentral and precentral-occipital leads, which indicated localization of pathologic changes in the right precentral area. The child continued to seem normal clinically, in spite of the persistent evidence of cortical abnormality in the right precentral area.

COMMENT

The crucial period of transition from the uterus to the outer world is fraught with peril to the unborn child, in spite of the margins of safety nature ordinarily interposes in all her processes. The feat of being born alive is no mean achievement when one considers how complex are the factors at play, and to be born physically and chemically intact is none the less remarkable for being so commonplace. It is not strange that birth injury, and especially damage to the brain, has always played a large role in the neonatal death rate. It has been repeatedly shown that the death rates in the first forty-eight hours of life have not been correspondingly reduced in relation to the great reductions in mortality rates thereafter. To launch a child properly into this world still remains the chief problem.

Considering the vast importance of the subject in terms of death or subsequent disability, one finds that much remains to be learned in regard to factors which affect the baby adversely as he passes through the birth canal. In many instances, the matter of a certain diagnosis of cerebral injury is no easy affair, in spite of the fact that some infants show unmistakable evidence. Any technic sharpening the diagnosis of cerebral damage will serve a most useful function. Our studies indicate that electroencephalography of the newborn may clarify the

diagnosis of cerebral damage and may even indicate cortical abnormalities in apparently normal newborn infants. So much more remains to be done in studying a far greater number of infants, especially in following them and their electroencephalographic activity over long periods, that no positive statements can be made at present regarding the prognostic import of abnormalities encountered in the newborn. Likewise, correlation of electroencephalographic findings with autopsy observations, both gross and microscopic, must be done on a large group of infants in order to verify the existence and localization of focal cortical abnormalities. The positive proof of cerebral damage and the localization of the site of injury may open the way to a reevaluation of therapy in infants with localized hemorrhage.

The use of electroencephalography in the study of clinical and subclinical cerebral damage is only a part of the potential advantages of the method. With the use of electroencephalography as a sensitive indicator of cortical damage, it is quite possible that more exact information can be obtained concerning certain factors in labor and delivery which affect the brain of the baby. Our studies showing the depressing effect "seconal sodium" has on cortical electrical activity of the newborn when given to the mother during labor [2] indicate a method of approach to the study of still other problems. Varying doses of different sedative, analgesic and anesthetic agents given to the mother need to be studied from the standpoint of their effects on the brain potentials of the newborn. A much more accurate knowledge might be obtained of the frequency with which cortical damage occurs as a result of such factors as the use of forceps, difficult delivery of the fetus, breech extraction, toxemia of pregnancy and a number of other conditions which are known to affect adversely at times the welfare of the baby. Thus, the application of the method may lead to further refinements in obstetric management, refinements which may conceivably influence favorably the still too high incidence of cerebral damage incurred in the birth process. With the exception of the studies on "seconal sodium," the use of electroencephalography of the newborn in evaluating obstetric hazards to the infant is an unexplored field. It should not so remain.

SUMMARY AND CONCLUSIONS

Abnormal electroencephalograms in 8 newborn infants are presented and analyzed. A wide variety of electroencephalographic abnormalities were encountered in this small group.

Seven of these infants showed clinical neurologic abnormality, while 1 of them was clinically normal.

In several of the infants the pattern of neurologic disorder was correlated with localizing electroencephalographic abnormalities. In some infants the electroencephalogram demonstrated cortical electrical abnormality before clinical symptoms and signs had been observed, and electroencephalographic abnormalities persisted in some of the infants after neurologic symptoms had disappeared.

Of special interest was the patient who showed electroencephalographic abnormalities while continuing to seem normal clinically. This indicates that electroencephalography of the newborn may detect cortical damage in the absence of clinical symptoms.

The sensitivity of the electroencephalogram in determining the presence of abnormal cortical electrical activity may well lead to a more definite realization of the incidence of cerebral damage in the birth process. By correlation of abnormal electroencephalographic findings with some of the factors at play in labor and delivery further refinements in obstetric management may well be evolved.

Dr. T. S. Hill, professor of psychiatry, University of Tennessee College of Medicine, and director, Gailor Psychiatric Hospital, and Dr. Hudson Jost, assistant professor of psychiatry and director, Psychophysiological Laboratories, Gailor Psychiatric Hospital, assisted in this study.

20 South Dunlap Street (3).

TREATMENT OF STAPHYLOCOCCIC PNEUMONIA AND EMPYEMA WITH PENICILLIN

Report of Six Cases, Two with Pulmonary Pneumatocele

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DURING the winter of 1944-1945, we had the opportunity of observing and treating with penicillin 6 infants and children suffering from staphylococcic infections of the lungs and pleura. Five of the patients had empyema, and the sixth had pneumonia without empyema. The course of the infections in these patients under penicillin therapy was so strikingly different from that observed in previous years that a brief review of each case is indicated.

Staphylococcic pneumonia constitutes a problem of major importance to the pediatrician. In the early stages, the differential diagnosis from pneumococcic pneumonia is extremely difficult. The disease is accompanied with a severe degree of toxemia, and, because of the tendency to form pulmonary abscesses rather close to the pleura, it is almost always complicated by empyema. These pulmonary abscesses also often involve small bronchi, and the bronchopleural fistulas produced thereby frequently give rise to a pyopneumothorax, which, if it is of the tension variety, becomes a real threat to the patient's life. The sulfonamide drugs are much less effective against the staphylococcus than against either the pneumococcus or the streptococcus; as a consequence, the relative incidence of staphylococcic empyema has increased in recent years. Before the advent of the use of penicillin, except for such general supportive measures as use of oxygen and blood transfusions, the pediatrician was left with surgical drainage as the only definite therapeutic measure for the treatment of this disease.

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A recent study by one of us (G. B. F.)[1] indicated that in the past the staphylococcus has accounted for 10 per cent of all cases of empyema in children, and that in infants under 1 year of age 45 per cent were of staphylococcic origin. Further, the disease carried a higher mortality in young infants, and thus any comparison of therapeutic regimens must take the age factor into consideration. A review of 186 cases of staphylococcic empyema from the literature revealed that the mortality for the entire pediatric age group was 39 per cent, while for infants under 1 year of age it was 45 per cent, and for those under 6 months of age, 51 per cent.

During the period from 1936 to 1944, prior to the present series of cases, 14 patients with staphylococcic empyema had been treated at the St. Louis City Hospital. Of these, 8 died, which is an over-all mortality rate of 57 per cent. On separating the patients into definite age groups, it was noted that all of the 8 patients under 6 months of age died, while the remaining 6 patients, whose ages ranged from 3 to 15 years, recovered. The use of either sulfathiazole or sulfadiazine for 9 of these patients did not influence the mortality. Autopsies were performed on the 8 who died. In each, there was an extensive pneumonic process with one or more pulmonary abscesses, which varied from 2 mm. to 2 cm. in diameter. A bronchopleural fistula could be demonstrated in 4 of the patients.

In order to illustrate in detail the course and treatment of staphylococcic pneumonia in the present series of penicillin-treated patients observed in the St. Louis City Hospital, the cases will be presented separately.

REPORT OF CASES

CASE 1.—D. H., an 18 day old white girl, was admitted on Dec. 17, 1944, with the chief complaint of grunting respirations for the preceding eighteen hours. Her previous health had been good.

Physical examination on her admission to the hospital revealed a well nourished, acutely ill infant, whose temperature was 39 C. (102.2 F.) and weight 3,570 Gm. She was pale, though not cyanotic, and exhibited rapid, grunting respirations. There were greatly diminished breath sounds and a dull percussion note over the entire right lung field. The white blood cell count was 26,000 per cubic millimeter, with a differential count of 3 juvenile cells, 12 stab forms, 69 polymorphonuclear leukocytes, 10 lymphocytes and 6 monocytes. The blood culture was sterile. The roentgenogram of the chest revealed pneumothorax on the right side with moderate collapse of the lung and a suggestion of fluid at the right costophrenic angle (fig. 1*A*).

Thoracentesis was immediately performed on the right side. In addition to a considerable amount of air under tension, 2 cc. of blood-tinged pus was with-

1. Forbes, G. B.: Diagnosis and Management of Severe Infections in Infants and Children: A Review of Experiences Since the Introduction of Sulfonamide Therapy; V. Staphylococcal Empyema; the Importance of Pyopneumothorax as a Complication, J. Pediat. **29**:45 (July) 1946.

drawn from the right pleural cavity. Hemolytic Staphylococcus aureus was cultured from this pus. This organism was coagulase positive, did not ferment mannite and was inhibited by 0.08 unit of penicillin [2] per cubic centimeter.

Treatment consisted of the oral administration of sulfathiazole in amounts of 0.2 Gm. per kilogram of body weight every twenty-four hours and of 10,000 units of penicillin administered intramuscularly every two hours. Closed intercostal siphon drainage of the right side of the chest was instituted shortly after the diagnostic thoracentesis, and a moderate amount of air bubbled out through the system. Twenty-five thousand units of penicillin was instilled into the thoracotomy tube daily for the first four days.

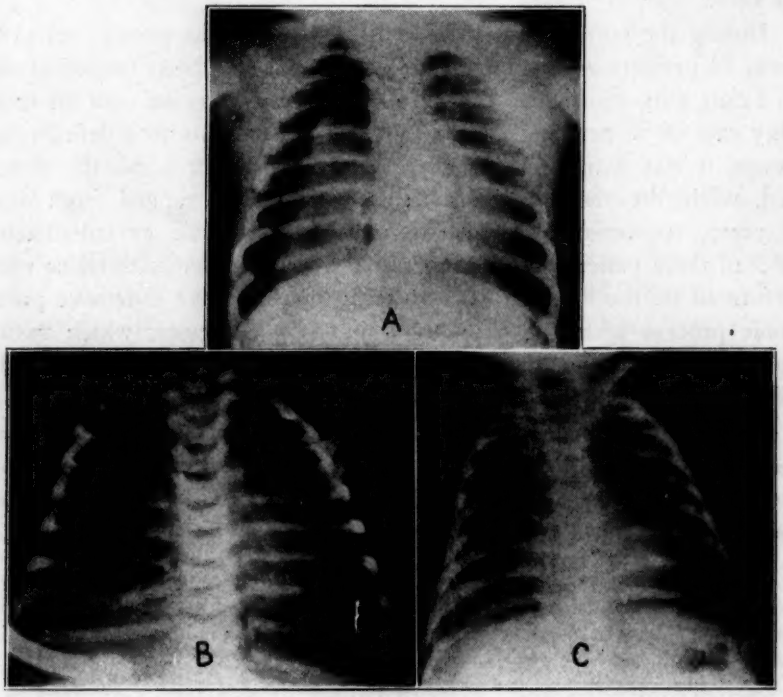

Fig. 1 (case 1).—(*A*) Roentgenogram taken on the day of admission revealed tension pneumothorax on the right, with a suggestion of fluid in the right costophrenic sinus. (*B*) After six days the lung had completely reexpanded under closed drainage, with slight thickening of the pleura. The solitary pneumatocele is evident. (*C*) At the end of three weeks the lung fields were essentially normal, with complete disappearance of the pneumatocele.

The baby's general condition improved rapidly, and her temperature fell slowly to normal on the fifth day in the hospital. Penicillin therapy was stopped on the seventh day and sulfathiazole at the end of the second week. Small amounts of

2. The tests for penicillin sensitivity of the infecting organisms and the determinations of penicillin concentration in the blood serum were performed by Dr. J. V. Cooke (A Simple Clinical Method for the Assay of Penicillin in Body Fluids and for the Testing of Penicillin Sensitivity of Bacteria, J. A. M. A. **127**:445 [Feb. 24] 1945).

pus continued to drain through the thoracotomy tube for the first week, but on the tenth day a roentgenogram of the chest showed good expansion of the right lung, and the drainage tube was removed.

Figure 1 *B* represents a roentgenogram taken on the fourth day in the hospital and shows a thin-walled, cystlike area in the midzone of the right lung field. This area was observed carefully on serial roentgenograms. Lateral views showed it to be in the lung itself, and not in the pleura. It gradually decreased in size and finally disappeared by the twenty-fifth day in the hospital. At no time did this "cyst" contain fluid; its walls were never thickened, nor was there evidence of reaction in the surrounding lung tissue.

The baby's convalescence was uneventful, and she gained 800 Gm. in weight before her discharge from the hospital, on the twenty-seventh day. A roentgenogram of the chest at this time revealed no abnormalities (fig. 1 *C*).

CASE 2.—C. F., a 3 week old white girl, was admitted on Jan. 8, 1945. Four days before admission she had become irritable, and two days later began to cough and to have fever and rapid respirations.

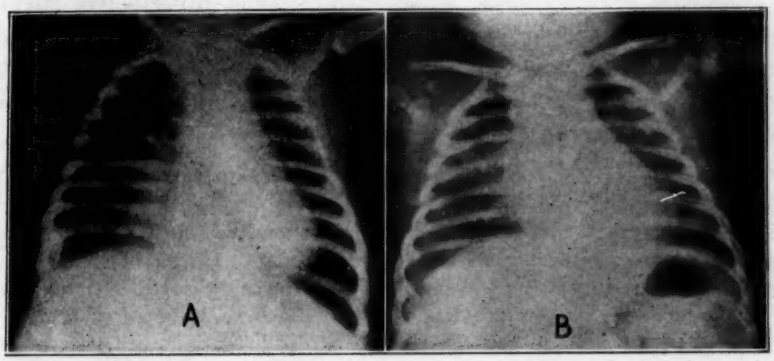

Fig. 2 (case 2).—(*A*) Roentgenogram taken on the day of admission revealed slight pneumothorax. (*B*) Two weeks later the roentgenogram of the chest was essentially normal.

Examination on admission revealed an acutely ill infant whose respirations were rapid and grunting in character. Her temperature was 38 C. (100.4 F.) and her weight 3,900 Gm. The percussion note was dull over the entire right side of the chest; diminished breath sounds and fine rales were heard at the base of the right lung. There was moderate distention of the abdomen. The white blood cell count was 20,400 per cubic millimeter, with a differential count of 2 eosinophils, 9 stab forms, 48 polymorphonuclear leukocytes, 37 lymphocytes and 4 monocytes. The blood culture was sterile. A roentgenogram of the chest showed pneumothorax on the right side with a slight shift of the mediastinum to the left, but with no definite evidence of pleural effusion (fig. 2 *A*).

Thoracentesis yielded a small amount of air and some thin pus, from which hemolytic Staph. aureus was cultured. Penicillin therapy, with injection of 10,000 units subcutaneously every two hours, was begun. Closed intercostal siphon drainage of the right side of the chest was instituted, with the recovery of considerable air and a small amount of pus.

The baby rapidly improved. Her temperature reached normal on the third day in the hospital, and roentgenograms of the chest showed rapid expansion of the right lung. Small amounts of air and pus continued to issue from the inter-

costal tube for the first few days, but improvement was so rapid that it was possible to discontinue both the penicillin therapy and the pleural drainage by the end of the first week. By the end of the second week the roentgenogram of the chest appeared normal (fig. 2*B*), and the baby had completely recovered. She was detained in the hospital another two weeks, however, because of occurrence of bilateral suppurative otitis media and parenteral diarrhea, for which sulfadiazine therapy was employed. She was discharged from the hospital on February 4, clinically well. When last seen in the outpatient clinic on April 17, she was asymptomatic and appeared healthy.

These 2 children were admitted to the hospital early in the course of their disease, and diagnosis was prompt, so that penicillin therapy could be employed early, and thus effectively. In each case the roentgenogram could have been interpreted as that of spontaneous pneumothorax, and a thoracentesis was necessary to make the diagnosis of empyema. As was pointed out in an earlier communication,[1] the occurrence of nontraumatic pneumothorax in an infant should immediately suggest the presence of staphylococcic pyopneumothorax. In each case, too, the early institution of closed intercostal siphon drainage not only provided for drainage of pus but also effectively relieved the pneumothorax and prevented its recurrence.

CASE 3.—B. H., a 3 year old white boy, was admitted to the St. Louis City Hospital on Dec. 12, 1944. Two days previously he had drunk about 1½ ounces (45 cc.) of a proprietary medicine, which contained camphor, cascara, sodium citrate and a large amount of ammonium and sodium salicylate. On the following day he began to vomit and cramping abdominal pain and fever developed. On admission to the hospital, his temperature was 38.9 C. (102 F.); he appeared acutely ill and had mild dyspnea. Physical examination revealed a reddened pharynx and an infected wound of the right palm. The abdomen was normal. Physical and roentgenographic examinations of the lungs showed no abnormalities. The white blood cell count was 14,100 per cubic millimeter, with a differential count of 1 basophil, 4 stab forms, 55 polymorphonuclear leukocytes, 36 lymphocytes and 4 monocytes. Additional blood studies showed that the reaction to the Kahn test was negative, the prothrombin time 93 per cent of normal and the carbon dioxide–combining power 39 volumes per cent; there was no salicylate in the blood.

The patient was given supportive therapy with fluids administered parenterally and was observed closely. On the third day in the hospital, his temperature, which had reached normal the day before, rose to 39 C. (102.2 F.), and an increased respiratory rate with a definite expiratory grunt and some abdominal distention developed. There were physical signs of consolidation of the lower part of the left lung field. The white blood cell count at this time was 17,900 per cubic millimeter. The blood culture was sterile.

The following day he appeared much worse and complained of pain in the left side of the chest and of abdominal discomfort. Severe diarrhea developed, and a Hiss Y strain of Shigella dysenterae was cultured from the stool. Despite therapy with sulfadiazine and succinylsulfathiazole U.S.P. (sulfasuxidine®), his temperature remained elevated and the pulmonary and gastrointestinal symptoms persisted.

On the fifth day in the hospital signs of an effusion in the left pleural cavity became evident, and thoracentesis yielded 25 cc. of thick pus, from which Staph. aureus was cultured. The organism was coagulase negative, did not ferment

mannite and was inhibited by 0.08 unit of penicillin per cubic centimeter. Intramuscular injections of penicillin were begun in doses of 10,000 units every two hours, and closed intercostal siphon drainage was instituted on the following day. Penicillin was instilled into the left pleural cavity daily in amounts of 25,000 units.

The boy now began to improve. His diarrhea subsided after three days, and succinylsulfathiazole therapy was discontinued. Penicillin was stopped on the fifteenth day of hospitalization and sulfadiazine on the twentieth day. Relatively little drainage of pus occurred through the thoracotomy tube, and at the end of the third week in the hospital, in view of the patient's excellent general condition and afebrile course for the preceding week, the tube was removed. Three days later his temperature had risen to 40 C. (104 F.), and roentgenograms of the chest suggested the presence of encapsulated pus in the upper part of the left lung field. Sulfathiazole therapy was begun, and a rib resection, with open drainage of the left side of the chest, was done, with the recovery of a moderate amount of pus. Hemolytic Staph. aureus was grown from the pus and also from a culture of blood taken at this time. The child's temperature fell promptly to normal; sulfathiazole was discontinued after ten days, and the remainder of his stay in the hospital was uneventful except for one episode of bilateral purulent otitis media, due to hemolytic Staph. aureus, which was successfully treated with sulfadiazine and myringotomy. He was discharged after a total stay in the hospital of eight weeks, in good general condition, with the drainage tube still in place.

The patient was followed closely for the next three months. Small amounts of pus continued to drain from the tube, and in March 1945 he was readmitted to the hospital for a series of penicillin irrigations. In April 1945, the tube was removed; the wound had healed nicely, and the roentgenograms of the chest showed only a slight residual pleural thickening on the left.

The course of the infection in this case was somewhat more protracted than in the first 2 cases, but the eventual outcome was just as satisfactory. Perhaps had the original thoracotomy drainage been converted to a thoracostomy drainage earlier, the flare-up which occurred, and which was obviously caused by the presence of undrained pus, could have been avoided. Penicillin, unfortunately, was not available in sufficient quantity on the latter occasion; but, even though bacteremia occurred, the combination of sulfathiazole therapy and adequate surgical drainage resulted in prompt improvement.

CASE 4.—D. L., a 2 month old white boy, was admitted on Dec. 9, 1944. He had been normal at birth, weighing 3,400 Gm., but had had intermittent episodes of vomiting and diarrhea since then and had failed to gain weight. Shortly before his admission, an infection of the upper respiratory tract developed, with cough, vomiting and diarrhea. The stools contained mucus and pus. On admission to the hospital, his weight was 2,860 Gm.; he appeared chronically ill and exhibited an infection of the upper respiratory tract and dehydration. There were no abnormal pulmonary signs. The diarrhea was gradually brought under control with the use of dietary measures, parenteral administration of fluids and blood transfusions, but the patient's general condition remained poor, and he gained no weight.

During the fifth week in the hospital, his temperature rose to 39.5 C. (103.1 F.), and a roentgenologic examination of the chest revealed a shadow in the right hilar region, which was interpreted as evidence of pneumonia. A blood culture at this

time was sterile. Sulfadiazine therapy was begun, but at the end of twenty-four hours the patient had become much more toxemic and dyspneic. The roentgenogram of the chest now revealed an opacity in the right cardiophrenic sinus with obliteration of the right costophrenic angle, suggesting pleural effusion. Later the same day a definite extension of the pleural effusion was noted in the roentgenogram of the chest, and thoracentesis yielded approximately 1 cc. of blood and pus. Culture of this fluid revealed Staph. aureus.

Penicillin therapy, 10,000 units given intramuscularly every two hours, was begun, and closed intercostal siphon drainage of the right pleural cavity was instituted. The tube functioned poorly, and the next day tension pneumothorax developed on the right, with displacement of the mediastinum to the left. This was relieved by thoracentesis and an adjustment of the intercostal tube, which now began to function properly. His temperature returned to normal, and, although he had a recurrence of diarrhea, his general condition improved somewhat. Seven days later a sudden episode of cyanosis and dyspnea occurred. Despite the fact that the intercostal drainage tube was functioning properly, with what appeared to be a normal fluctuation of the water level in that portion of the tube attached to the receiving bottle, fluoroscopic examination demonstrated the presence of tension pneumothorax on the right, with displacement of the mediastinum to the left. Although his symptoms were successfully relieved by the aspiration of a large amount of air from the right pleural cavity, and the intercostal drainage system continued to function properly, tension pneumothorax recurred within a few hours. Since it was evident that the pleural space was not being drained adequately, a second thoracotomy was performed above the site of the first and closed siphon drainage instituted at this point also. Considerable amounts of air rushed forth from the second intercostal drain. Despite the fact that both closed drainage systems now worked well, the patient became rapidly worse; respirations were irregular, and he died shortly. A postmortem roentgenogram of the chest revealed several small areas of destruction in the lower lobe of the right lung and slight pneumothorax on the right side. Permission for autopsy was not obtained.

CASE 5.—J. S., a 3 month old white girl, was admitted on March 9, 1945. The baby had had a mild infection of the upper respiratory tract for the preceding week but had no alarming symptoms until five hours prior to admission. At that time fever and rapid, grunting respirations developed.

Examination on her admission to the hospital revealed that she was acutely ill. Her temperature was 39.6 C. (103.3 F.) and her weight 5,800 Gm. She was dyspneic but not cyanotic. Both tympanic membranes were reddened and bulging. Moist rales were heard over the bases of both lungs posteriorly, and the breath sounds were slightly diminished at the tip of the left scapula. The white blood cell count was 16,000 per cubic millimeter, with a differential count of 12 stab cells, 60 polymorphonuclear leukocytes, 20 lymphocytes and 8 monocytes. The blood culture was sterile.

Sulfadiazine therapy was begun. A bilateral myringotomy on the following day yielded a small amount of purulent material, from which hemolytic Staph. aureus was cultured. The temperature remained elevated, and by the third day in the hospital the baby's dyspnea had become much worse, and she was cyanotic. A roentgenogram of the chest revealed a uniform haziness of the entire left lung field, with a slight displacement of the mediastinum to the right.

Thoracentesis on the left side yielded 20 cc. of yellowish red pus, from which hemolytic Staph. aureus was cultured. This organism was coagulase negative, did not ferment mannite and was inhibited by 0.06 unit of penicillin per cubic centimeter. Closed intercostal siphon drainage was immediately instituted, and at

the time the thoracotomy was performed an additional 30 cc. of pus and a small amount of air issued from the chest. The baby experienced immediate relief of cyanosis and dyspnea from this procedure. Penicillin therapy was also begun at this time, 5,000 units being given intramuscularly every two hours.

The thoracotomy tube functioned poorly because of plugging of the opening with large fibrin clots, which continued to form despite daily irrigations with penicillin and saline solution. However, the patient began to improve, and her temperature fell gradually to normal by the end of the first week in the hospital. Several transfusions of whole blood were given during this period. The left lung failed to expand properly, but in view of the continued normal temperature, penicillin therapy was discontinued on the seventeenth day of hospitalization.

Three days later the baby again had a high fever and became more dyspneic. The discharge from the chest became foul, and culture revealed both hemolytic Staph. aureus and Pseudomonas aeruginosa (Bacillus pyocyaneus). She began to have severe diarrhea and frequently required parenteral administration of fluid. Penicillin therapy, 10,000 units given subcutaneously every two hours, was resumed. A rib resection was done, and open drainage of the left side of the chest was instituted. The temperature returned to normal; but the patient grew rapidly worse, became extremely dyspneic and pale and died on the twenty-sixth day of hospitalization. Several cultures of blood taken during the last two weeks of life were sterile.

At autopsy the left lung was observed to be collapsed and noncrepitant and the pleura thickened. The left pleural cavity contained only a few cubic centimeters of thick, yellow pus. There was an abscess cavity, 1 cm. in diameter, in the upper lobe of the left lung, very close to the interlobar fissure. Microscopic examination revealed a fibrinous, purulent pleural exudate; throughout the lung substance there were many areas of tissue destruction, with considerable fibrinous exudate and infiltrations with numerous mononuclear cells. The right lung and its pleura appeared normal. The pericardial cavity contained about 15 cc. of cloudy yellow fluid, and the epicardium was covered by a fibrinous exudate. Culture of the pericardial fluid was sterile.

These 2 cases represent failures in treatment which occurred despite the early institution of penicillin therapy and surgical drainage in each. In the former, we believe that severe malnutrition (weight at 3 months of age approximately 600 Gm. below weight at birth) was an important factor in the fatal outcome. In view of a normally functioning closed intercostal drainage system, the repeated occurrence of tension pneumothorax in this case is puzzling, and it is unfortunate that we were not permitted to perform an autopsy. It is quite possible that the bronchopleural fistula was of such dimensions that the intercostal tube was too small to effect removal of air from the pleural cavity rapidly enough to prevent a gradual building up of intrapleural tension. We have noted such extensive bronchopleural communications previously. In 1 case, not in the present series, in which autopsy was performed several years ago, the opening into the pleural cavity measured 2 cm. in diameter. Another possibility is that there were multiple abscesses in the right lung which formed more than one bronchopleural fistula, and that there were at least two areas of pneumothorax, separated by pleural adhesions.

In the latter of these 2 cases, penicillin therapy did not seem adequate to arrest the infection. Whereas the infecting organism was inhibited by 0.06 unit of penicillin per cubic centimeter, blood levels of 0.8 and 0.4 unit of penicillin per cubic centimeter of blood were attained one and two hours, respectively, after the subcutaneous injection of 10,000 units of penicillin in this case. Despite the fact that the patient received, at least during the last week of her illness, penicillin in amounts far above that necessary to kill the infecting organism, the cultures of empyema pus continued to yield the pathogen, and the lung showed evidence of active disease at the time of autopsy. The concentration of penicillin in the blood was not determined during the period in which the patient was given 5,000 units subcutaneously every two hours, and it must be admitted (although it is unlikely in view of the foregoing data) that the blood levels during that time may have been sufficiently low to permit the development of resistance to penicillin in the organism. The occurrence of pericarditis and the failure of the affected lung to expand properly were also major factors in the fatal outcome in this case.

CASE 6.—G. C., a 4 week old white boy, was admitted on Jan. 30, 1945, for observation relative to the mother's statement that he had vomited most of his feedings during the previous week and that the vomitus contained blood. Examination revealed scaphocephaly but nothing else remarkable. During the first six days in the hospital the baby did fairly well; and, although he continued to vomit occasionally, hematemesis was not observed.

On the seventh and ninth days in the hospital he had a transient elevation of temperature to 38.0 C. (100.4 F.) but exhibited no other abnormalities. On the twelfth day his temperature rose again, and he had a sudden episode of pallor and shallow, irregular breathing. The breath sounds were greatly depressed over both posterior lung fields, but the percussion note was normal. The roentgenogram of the chest showed a definite area of consolidation in the lower part of the right and the upper part of the left lung fields (fig. 3*A*). The patient was immediately placed in an oxygen tent and therapy with sulfadiazine and penicillin (10,000 units intramuscularly every two hours) was begun. The following day the temperature dropped to normal, but the baby had a severe collapse, during which he ceased to breathe and the heart sounds became inaudible. He was revived with the aid of epinephrine given intracardially and artificial respiration. Culture of blood taken on this day revealed hemolytic Staph. aureus.

The baby's condition remained critical, and continuous oxygen therapy was required. Repeated roentgenograms of the chest were made, and the areas of consolidation were seen to resolve slowly. On February 19 a roentgenogram (fig. 3*B*) for the first time revealed several pneumatoceles in the left lung field and in the lower third of the right lung. These were observed carefully by serial roentgenograms, and at no time did they contain fluid or show any evidence of reaction in the adjacent lung tissue. On February 17, the baby had an episode of bilateral suppurative otitis media.

During the first week in March, the patient began to improve slowly. Penicillin therapy was discontinued on March 17, and, although several large pneumatoceles were now visible in each lung field (fig. 3*C*), no respiratory difficulty was

observed at this time. The child began to gain weight, had no further gastrointestinal symptoms and was discharged on May 20 in good general condition (fig. 3*D*).

The baby was carefully followed in the outpatient clinic. By the end of July 1945 the pneumatoceles on the right had disappeared, and by November 1945 those on the left were also gone. He remained asymptomatic and weighed 12.3 Kg. on Jan. 14, 1946.

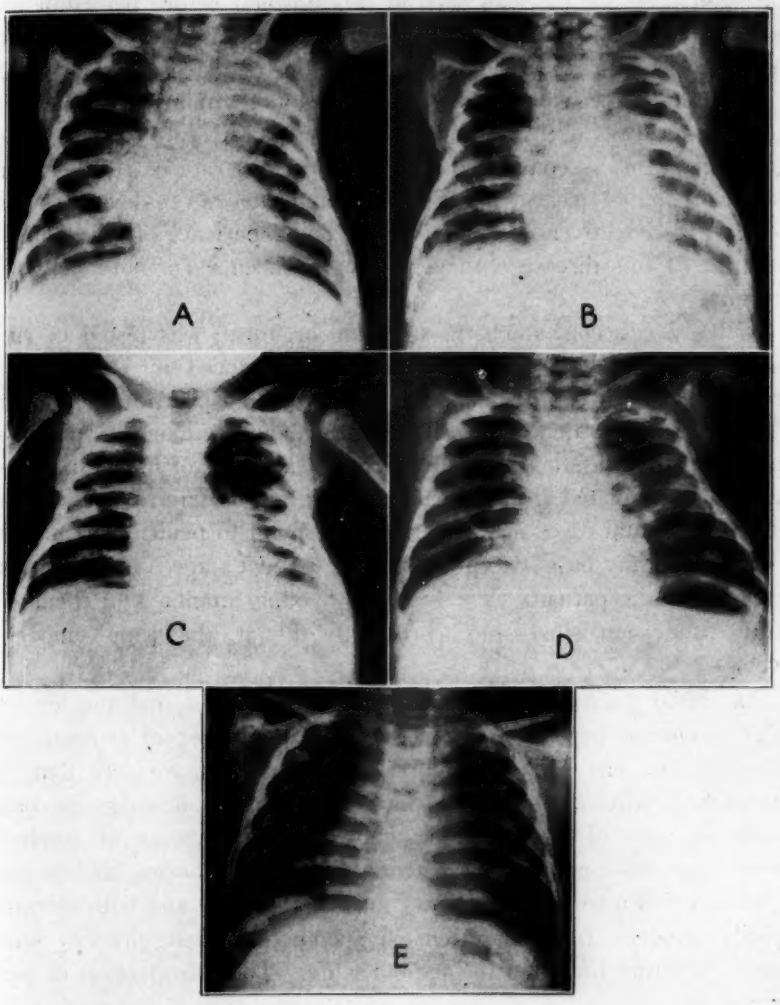

Fig. 3 (case 6).—(*A*) Roentgenogram taken on the twelfth day in the hospital shows uniform consolidation of the upper third of the left lung field with patchy consolidation of the lower third of the right lung. (*B*) On the seventeenth day numerous small pneumatoceles are present in the left lung and in the lower half of the right lung. (*C*) On the thirty-fifth day there is extensive formation of pneumatoceles bilaterally. (*D*) On the ninety-fifth day several large pneumatoceles are still present. (*E*) Roentgenogram taken one year later shows normal lung fields.

We believe that this case represents an instance of staphylococcic pneumonia. The fact that empyema did not develop, as it has with great regularity in the past, is a good indication of the effectiveness of penicillin as a therapeutic agent.

COMMENT

The more favorable course in these cases with penicillin therapy, as contrasted with the 14 cases seen at this hospital before penicillin was available, is immediately apparent. Instead of an over-all mortality rate of 57 per cent, the rate for the penicillin-treated patients was only 33 per cent. Moreover, in the group of young infants, in which the disease has always been more serious, the mortality rate for this series was 40 per cent, as contrasted with the previous rate of 100 per cent. The fact that in 1 patient in this series empyema never developed also attests to the effectiveness of penicillin. The experience of others in the treatment of this disease with penicillin has been even more favorable than ours.[3]

Of the 3 cases in which the infecting organism was tested in vitro against penicillin, complete inhibition was produced by 0.08 unit of penicillin per cubic centimeter in 2 and by 0.06 unit per cubic centimeter in the other. This degree of sensitivity is about the average which has been observed in a study of the penicillin sensitivity of many strains of staphylococci isolated from human material.[4] The failure of the infection in the 2 fatal cases in this series to respond to penicillin is difficult to explain on any basis except that of the patient's age. In addition to the fact that the patients were both very young infants, 1 of them was greatly undernourished and chronically ill at the time empyema developed.

An initial pneumothorax was present in 2 cases, and the air was under moderate tension in 1 of them. The danger of tension pyopneumothorax has been so impressed on us that we feel that the immediate institution of closed intercostal siphon drainage is paramount in cases of staphylococcic empyema. Each case of staphylococcic empyema constitutes a potential pyopneumothorax, and because of the fact that a pyopneumothorax may at any time, and with alarming rapidity, progress to massive tension pneumothorax the process constitutes a potential threat to the patient's life. The introduction of peni-

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3. Philips, B., and Kramer, B.: Chemotherapy of Staphylococcus Aureus Infection of the Lung and Pleura in Infancy, J. Pediat. **26**:481 (May) 1945. McBryde, A.: Hemolytic Staphylococcus Pneumonia in Early Infancy: Response to Penicillin Therapy, Am. J. Dis. Child. **68**:271 (Oct.) 1944. Davis, W. S.; Hyman, M. E., and Ruhstaller, F. D.: Penicillin as an Aid in the Treatment of Primary Staphylococcus Pneumonia with Empyema, J. Pediat. **30**:55 (Jan.) 1947.

4. Cooke, J. V.: Personal communication to the authors.

cillin raised the hope that perhaps surgical drainage could be dispensed with in cases of empyema and the patient adequately treated by thoracentesis alone. Several observers have noted that under such a treatment regimen there is a tendency in many cases to the formation of a thick fibrinous pleural membrane, requiring surgical drainage for complete cure.[5] For the aforementioned reasons, then, we believe that surgical drainage still forms an important role in the therapy of staphylococcic empyema.

The "cystlike" areas in the lung present in cases 1 and 6 are probably pulmonary pneumatoceles, as described by Peirce and Dirkse.[6] Benjamin and Childe [7] used the term "localized bullous emphysema" to describe the same thing. The initial formation of these pneumatoceles is one of a persistent check valve obstruction of a bronchiole in an area of pneumonia. That they were located within the lung parenchyma in our cases was substantiated by lateral roentgenograms. In case 6 the formation of the pneumatoceles was progressive, even though the infant was clinically well, suggesting that subsequent to their initial formation in an area of pneumonia, others may be formed as the result of pressure on neighboring bronchioles. In case 1 only a solitary pneumatocele formed. This disappeared over a period of three weeks, while in case 6 multiple pneumatoceles were present for nine months after their initial appearance. The experience of Almklov and Hatoff,[8] in which pneumatoceles were observed in 7 of 50 children with various types of pneumonia during a one year period, indicates that this condition may occur more frequently than is commonly realized.

Case 6 illustrates well the rapidity with which the symptoms of staphylococcic pneumonia can develop, and the overwhelming initial toxemia which may be produced. Radical resuscitation, with the administration of epinephrine intracardially, was necessary to prevent death in this child. In former years, before penicillin was available, several patients in St. Louis City Hospital succumbed within forty-eight hours after the onset of symptoms, treatment being of no avail. It is obvious that only early diagnosis and prompt intensive penicillin therapy will save these patients in the future.

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5. Poppe, J. K.: The Limitations of Penicillin in Treating Empyema, J. A. M. A. **129**:435 (Oct. 6) 1945. Blades, B.; Hamilton, J. E., and Dugan, D. J.: Observations on the Treatment of Empyema Thoracis with Penicillin, Surgery **17**:572 (April) 1945.

6. Peirce, C. B., and Dirkse, P. R.: Pulmonary Pneumatocele (Localized Alveolar or Lobular Ectasia): Certain Considerations in Cystic Disease of Lung, Radiology **28**:651 (June) 1937.

7. Benjamin, B., and Childe, A. E.: Localized Bullous Emphysema Associated with Pneumonia in Children, J. Pediat. **15**:621 (Nov.) 1939.

8. Almklov, J. R., and Hatoff, A.: Pneumatocele During the Course of Pneumonia in Children, Am. J. Dis. Child. **72**:521 (Nov.) 1946.

SUMMARY

Six cases of staphylococcic infection of the lung, observed at St. Louis City Hospital during the winter of 1944-1945, are presented, in 5 of which unilateral empyema was present. Intensive penicillin therapy was employed in all, and closed intercostal siphon drainage in the 5 cases of empyema.

During the period from 1936 to 1944, the mortality at this hospital for this disease had been 57 per cent for children of all ages and 100 per cent for young infants. In the present series of penicillin-treated patients these mortality rates were 33 and 40 per cent, respectively.

In 2 cases pyopneumothorax was present on the patient's admission to the hospital, and the air was under considerable tension in 1 of them.

In 2 cases pulmonary pneumatoceles were associated with the pneumonic process; the pneumatoceles disappeared in three weeks in 1 case and after nine months in the other case.

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PREVENTION OF FETAL ANOXIA

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IT IS COMMON KNOWLEDGE that anoxia and advanced degrees of hypoxia are frequent causes of stillbirth and neonatal death. Oxygen want on the part of the fetus may be brought about by several mechanisms.

The term anoxic anoxia (anoxia due to lack of oxygen) may be defined as deficiency of oxygen in the tissues due to some cutting off or vitiation of the oxygen supply to the blood. In extrauterine life this source of supply is, of course, the respiratory tract. As examples of anoxic anoxia may be cited laryngeal obstruction and the effects of high altitude flying. Since the fetus in utero derives its oxygen from sources outside its own body, indeed from the oxygen in the maternal blood some distance from its own body, a breakdown in this extrinsic oxygen supply must be considered in anoxic anoxia of the fetus. In the opinion of Edith Potter, only cases resulting in death in this group are justifiably called "anoxic," and rightly so, because in such fatalities oxygen lack is the primary and, ordinarily, the sole determining factor in the outcome, and death is simply the result of outright asphyxiation. Other types of intrauterine anoxia are secondary to various intrinsic disturbances of the fetus and do not act singly.

The fetus in utero may have anoxic anoxia from a variety of causative factors as shown in the table. This type of oxygen lack in the fetus may be subdivided into two main etiologic groups. In one, reduction in the oxygen tension of maternal blood is responsible, while in the other the determining cause is some kind of interference with the passage of oxygen from mother to fetus.

As the commonest cause of anoxic anoxia of the fetus, I should incriminate reduction of the oxygen pressure in the maternal blood due to administration of asphyxiating anesthetics, especially nitrous oxide. Nitrous oxide–oxygen anesthesia for periods of less than three minutes and in proportions of 85 to 15 or weaker does not cause a harmful degree of anoxemia. The time element is most important. Pure nitrous oxide administered for four or five breaths to produce analgesia may cause less anoxemia than a mixture of 85 parts nitrous oxide to 15

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This paper and the three papers following it were read before the joint meeting of the Section on Obstetrics and the Section on Gynecology at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 25, 1948.

parts oxygen continued for three minutes. On the other hand, there is abundant evidence to show that when nitrous oxide and oxygen are given in concentrations of 90 to 10 or stronger over periods which exceed three minutes advanced degrees of anoxia are produced in about 1 infant in 3. It is not intended by this statement to advocate exclusion of nitrous oxide–oxygen anesthesia entirely from the field of obstetrics. The criticism is only of the administration of concentrated mixtures without ether for periods which exceed two or three minutes. An adequate saturation of the fetal blood with oxygen can be guaranteed only if the mother receives at least 15 parts of oxygen in every 100 parts of the gas mixture. To satisfy this end, ether should be added to the mixture if the proportion of 85 to 15 does not suffice. After prolonged labors in particular, babies withstand anoxia poorly. If operative delivery is anticipated, some type of anesthesia should be employed other than nitrous oxide and oxygen with its well known potentialities for asphyxiation. In sum, in my opinion, the only safe

Causes of Anoxic Anoxia of the Fetus in Utero

I. Causes due to changes in the maternal blood
   A. Asphyxiating anesthetics (nitrous oxide)
   B. Anesthetic agents or other factors which depress the maternal blood pressure (spinal and caudal anesthesia)
   C. Systemic diseases (such as heart failure and pneumonia)
II. Causes due to interference with passage of oxygen from mother to fetus
   A. Abruptio placentae; infarcts
   B. Prolapse of cord; knots in cord
   C. Tetanic uterine contractions caused by posterior pituitary injection U. S. P. ("pituitrin")

use of mixtures of gas and oxygen (without ether) in labor is by the *à la reine* technic, that is, the nitrous oxide–oxygen mixture is given with each contraction, with removal of the mask between pains. Because of the time factor incident to actual delivery and the high concentration necessary to obliterate pain over that interval, it is not safe for actual delivery, at least when any substantial degree of anesthesia is sought.

Another way in which anesthetic agents admininstered to the mother may bring about anoxic anoxia in the fetus is through the depression of maternal blood pressure which frequently follows spinal and caudal anesthesia. In a recent study by Andros and associates [1] at the Chicago Lying-In Hospital of the University of Chicago, based on 719 cases in which saddle block anesthesia was used, the systolic blood pressure fell below 80 mm. of mercury for a recordable period in 13.7 per cent. This fall below 80 mm. of mercury was of less than five minutes' duration in 51 per cent of the cases and lasted ten minutes

1. Andros, G. J.; Dieckmann, W. J.; Ouda, P.; Priddle, H. D.; Smitter, R. C., and Bryan, W. M., Jr.: Spinal (Saddle Block) Anesthesia in Obstetrics, Am. J. Obst. & Gynec. **55**:806, 1948.

or less in 75 per cent. Hingson and his associates reported a similar depression of the blood pressure in 10 per cent of 2,457 patients receiving continuous caudal analgesia at the Lying-In Hospital, Philadelphia. These authors [2] stated, furthermore, that whenever the maternal blood pressure remains below 80 mm. of mercury systolic for several minutes during labor the resting and contracting uterine tone is conceivably greater than the arterial pressure. They found that fetal anoxia is demonstrable in almost every case in which this condition is allowed to exist for five minutes or longer. However, this hazard to the fetus in association with spinal and caudal anesthesia is by no means to be construed as an indictment of these procedures, since they possess advantages to the infant which outweigh the dangers of the fall in blood pressure. From the standpoint of the prevention of fetal anoxia, the most important thing to know about the behavior of blood pressure with these anesthetics is that such falls are readily amenable to correction, provided the attending physician is aware of their frequency and alert to take steps to correct the circulatory depression. Blood pressure readings must be routine, before the administration of these anesthetics and subsequently every two or three minutes.

Dripps [3] stated: "Spinal anesthesia by pooling blood in the periphery, by dilating veins and decreasing venous pressure can be regarded as a bloodless phlebotomy. . ." Caudal anesthesia has a similar effect. Since with these agents the blood has a tendency to become pooled in the peripheral veins, raising the legs acts as a sort of autotransfusion. Therefore, if any appreciable drop in the blood pressure occurs, the legs should be elevated immediately, a procedure which will allow blood pooled in the extremities to return to the heart. This measure alone is often enough to correct the circulatory depression promptly, but it should be accompanied with immediate oxygen therapy, as well as the intravenous injection of a vasopressor drug.

From time to time certain systemic diseases of the mother, such as heart failure, pneumonia or profound anemia, may likewise result in a diminution in oxygen supply to the fetus, but these conditions represent a much rarer cause of fetal anoxia than do the factors already discussed. It goes without saying, however, that pregnant women with such systemic diseases should have appropriate oxygen therapy because any visible degree of cyanosis in the mother is invariably associated with a much greater degree of anoxia in the fetus and one which may be fatal.

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2. Hingson, R. A.; Edwards, W. B.; Lull, C. B.; Whitacre, F. E., and Franklin, H. C.: Newborn Mortality and Morbidity with Continuous Caudal Analgesia, J. A. M. A. **136**:221 (Jan. 24) 1948.

3. Dripps, R. D.: Circulatory Changes During Spinal Anesthesia: Their Physiological Basis, S. Clin. North America **26**:1377, 1946.

In fetal anoxia due to interference with the passage of oxygen from mother to fetus, the commonest cause is probably premature separation of the placenta, or abruptio placentae. The high toll in fetal life which this complication exacts is shown by the fact that the fetal mortality rates reported range from 65 to 90 per cent. Even those infants who are born alive frequently die during the first few days because of irreversible cerebral damage sustained during the period of intrauterine anoxia. In the present state of knowledge little can be done to prevent fetal deaths from this cause. The same may be said of massive placental infarction, a less common cause of anoxia.

Prolapse of the umbilical cord occurs once in every 150 deliveries, approximately, and about half the infants die as the result of anoxic anoxia. Space does not allow me to discuss the management of this complication. It is perhaps enough to say that, regardless of the treatment, it is unlikely that any substantial improvement in fetal prognosis following this accident can be anticipated, provided the mother's welfare is also considered. Nor does space permit discussion of the last cause of anoxic anoxia listed in the table, tetanic uterine contractions. In connection with pituitary extract, it will suffice to recall that its use prior to the birth of the baby should be rigidly restricted to cases of true uterine inertia, with no disproportion, that a single dose should never exceed 1 minim (0.06 cc.) and that, even then, the drug is not without its dangers.

In addition to anoxic anoxia, the fetus may, and frequently does, have stagnant anoxia consequent on cerebral injury. As was shown by Schnedorf and his associates,[4] concussion of the brain, with or without skull fracture, causes a depression of oxygen in arterial blood from 5 to 44 per cent. Here, the supply of oxygen is adequate, but its transportation to the tissues by the blood stream is sluggish, owing presumably to cerebral edema and injury to the vasomotor center. Apparently then in this type of anoxia the main injunction is to avoid trauma. The midforceps operation alone carries with it a 30 per cent mortality to the infant—a figure not to be countenanced in modern obstetrics.

In addition to intrauterine anoxia, oxygen deficiency in the first hours or days of life is often the result of improper management of labor. Especially costly in terms of fetal outlook is the mismanagement of premature labor. Patients in premature labor should be permitted no form of analgesia except continuous caudal or spinal anesthesia. I have found continuous caudal anesthesia ideal. Likewise, the delivery should be effected by caudal, spinal or local infiltration anesthesia and preceded by a liberal median episiotomy. In my opinion, the best way

4. Schnedorf, J. G.; Munslow, R. A.; Crawford, A. S., and McClure, R. D.: Anoxia and Oxygen Therapy in Head Injury, Surg., Gynec. & Obst. **70**:628, 1940.

to effect delivery of a premature infant—especially a small one—is as follows: With the head on the perineum and the vulvar ring just beginning to distend, a median episiotomy is made, and this is followed by gentle fundal pressure. This procedure usually suffices for most cases, but with some of the larger premature infants, gentle extraction with forceps may be advisable. When possible, I prefer spontaneous delivery assisted by fundal pressure to the use of forceps. The cord should not be clamped until pulsations cease, since these infants, because of their tendency to become anemic, need all the blood they can get. The infant now becomes a pediatric problem, but it should be remembered by obstetricians, as well as pediatricians, that the main immediate desiderata are: a clear airway, oxygen, warmth and as little handling as possible.

FETAL ANOXIA AT BIRTH AND CYANOSIS OF THE NEWBORN

Differential Diagnosis and Management

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ANOXIC INJURY is the primary cause of 60 per cent of deaths among full term and premature infants and of at least as high a proportion of neonatal morbidity. Anoxia may occur in utero at any time; it always occurs to some degree during the birth process, and it may develop after birth. The oxygen lack may be an isolated episode; it may be intermittent or continuous and of greater or less severity and duration. The condition is an overwhelming force that affects every organ and tissue of the body to a variable and unpredictable degree. The chaotic collection of clinical symptoms that oxygen lack can produce becomes better understood when these variables are considered and when the physiologic and pathologic changes produced by anoxia are appreciated.

Anoxia may produce an increased hydrogen ion concentration through an accumulation of carbonic and lactic acids. This acidosis in turn may result in the progressive states of excitation, discharge of energy and, finally, exhaustion or paralysis of nerve tissue. The acidosis may produce loss of tone and dilatation of heart muscle, as well as loss of tone, dilatation, liberation of plasma and hemorrhage in blood vessels. The progressive pathologic changes that may be caused by anoxia can be summarized as congestion, edema, hemorrhage and death of tissue.

FETAL ANOXIA LATE IN PREGNANCY

Severe fetal anoxia may occur some days or weeks prior to birth, producing a characteristic clinical syndrome that can be recognized instantly at birth by the golden yellow of the amniotic fluid and vernix caseosa and a yellow staining of the infant's skin and nails. The occurrence of this syndrome is not rare—my associates and I encounter it approximately 6 times per thousand births. The recognition of the syndrome is important, since the group collected on the basis of the presence of this one condition at birth had a mortality rate of 12 per cent and a high morbidity rate. Twenty per cent of the group had

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the icterus gravis type of erythroblastosis fetalis,[1] with a mortality rate of 36 per cent. The remaining 80 per cent of the group had a mortality rate of 6 per cent.

The principal cause of intrauterine anoxia is stated to be disease of the placenta. Eighty-six per cent of the placentas in the erythroblastotic group showed increased size of villi, syncytial degeneration, epithelial vacuolization, hyperplastic or edematous stroma, diminution of vessels and nucleated red blood cells. Eighty per cent of the placentas in the nonerythroblastotic group showed evidence of premature separation: old focal necrosis with calcification in the decidua, antepartum necrosis of many villi, decidual necrosis with obliteration of the fetal vessels, thrombosis of the decidual sinusoids, chorionitis with a loose, edematous chorionic plate containing a large number of monocytic cells, the cytoplasm of which showed a fine brown pigment, probably hemosiderin, or massive hemorrhage in the stroma of the

Clinical Symptoms in Babies with Yellow Vernix

	Group with Icterus Gravis, %	Group Without Icterus Gravis, %
Resuscitation required	27	28
Grunting, labored respiration	60	23
Cyanosis	30	19
Convulsions	30	6
Hypertonia	40	6
Hypotonia	10	17
Extensive petechial hemorrhage	10	11
Gastrointestinal bleeding	0	11

cord with slight edema and hypoplasia of the placenta. In both groups the placenta membranes and umbilical cords were stained deep green.

One half of the mothers had recognized complications of pregnancy, including erythroblastosis (20 per cent), postmaturity (12 per cent), toxemia (7 per cent), repeated unsuccessful attempts at external version (5 per cent) and premature separation of the placenta, latent syphilis or chronic bronchiectasis (5 per cent).

The clinical symptoms, except those resulting directly from erythroblastosis and attributable to anoxic injury, are strikingly similar in the two groups of babies with yellow vernix—those with and those without icterus gravis.

FETAL ANOXIA DURING DELIVERY

The symptoms of fetal distress caused by anoxia during labor are well recognized. An acceleration of the fetal heart rate is usually the result of mild anoxia, while a slowing of the heart rate is an

1. The presence of yellow vernix is not pathognomonic for erythroblastosis fetalis as 60 per cent of this series of erythroblastotic infants did not have yellow vernix.

ominous sign of severe anoxia. In vertex presentations severe anoxia is also evidenced by the passing of meconium.

The possible causes of fetal anoxia are legion—anything that diminishes the oxygen supply to the maternal side of the placenta and any interference with the placental or cord circulation may interfere with the oxygen supply to the fetus.

The treatment of fetal distress calls for the utmost in obstetric skill. The cause must be determined as rapidly as possible, frequently by a scientific guess. Corrective measures must be instituted, and, if relief is not obtained, delivery as rapidly as it can safely be accomplished may be indicated. For both prophylaxis and treatment, the practice of giving the mother inhalations of pure oxygen during the latter part of labor is being increasingly advocated.

NEONATAL ANOXIA

At birth the newborn child must satisfy immediately his own oxygen requirement through a new and untried anatomic and physiologic system. The control of this system rests in the respiratory centers, backed up by the emergency carotid and aortic chemoreceptors. These centers may have been damaged by anoxia either in utero or during delivery, by actual traumatic injury during birth, by the direct effects of maternal analgesia or anesthesia or by any combination of these various factors. Any interference with the establishment of normal respiration at birth may continue preexisting anoxia or initiate extrauterine anoxia.

In addition to failure of the respiratory center to function, extrauterine anoxia may be due to mechanical obstruction of the airways from aspirated fluid, blood, mucus, vernix or meconium. It may be due to pathologic changes in the lungs secondary to intrauterine anoxia or to congenital malformation of the lungs, trachea, bronchi or diaphragm. Extrauterine anoxia may also result from certain congenital malformations of the heart and blood vessels.

RESUSCITATION OF THE NEWBORN

Most authors have abandoned the time-honored terms of asphyxia pallida and asphyxia livida in favor of some modification of Flagg's [2] classification to describe the degree of asphyxia exhibited by the newborn infant at birth.

1. *Mild Asphyxia.*—Breathing does not take place within thirty seconds of the birth of the head. The muscle tone is good. The infant resists movements of the head and limbs. Conjunctival and

2. Flagg, P. J.: Treatment of Postnatal Asphyxia, Am. J. Obst. & Gynec. **21**:537-541, 1931.

gag reflexes are present. The heart rate is normal or rapid. Amniotic fluid and mucous plugs may fill the airways. In this group, truly asphyxiated babies must be separated from those simply anesthetized or narcotized by maternal analgesia or anesthesia.

2. *Moderate Asphyxia.*—The muscle tone is poor or absent. There is no resistance to opening the mouth. No reflex irritation is induced by aspiration or by stimulation of the glottis. The heart rate is rapid and soon slows ominously.

3. *Severe Asphyxia.*—The infant does not respond to attempts at resuscitation. He appears livid or pallid. There is absence of any respiratory movement. Only an occasional flicker of the cardiac impulse may be detected through the thoracic wall.

The appraisal of the infant's condition at birth has been complicated by the advent of the various methods of obtaining maternal analgesia and anesthesia. When babies were delivered naturally, 90 to 95 per cent cried and breathed spontaneously at birth. All workers agree that maternal analgesia and anesthesia result in a high incidence of "slow" babies. The incidence is directly proportional both to the amount of drug given and to the duration of analgesia. It is also influenced by the drug or combination of drugs administered. This "slowing" of the babies is unfortunate, but it is made worth while by the benefits the infants gain as the result of analgesia. An ideal method of maternal analgesia has not been discovered as yet.

Cole [3] reported that with satisfactory analgesia 75 per cent of all newborn infants will possess an intact central nervous mechanism and will spontaneously initiate extrauterine respiration within thirty seconds of the birth of the head. These infants make their initial gasp within two seconds, cry within five seconds and have established regular respiration within ten seconds of the time the head is born. He contended that a delay for as long as thirty seconds is definitely abnormal and, in most instances, can be traced to some known factor. He observed that 10 per cent of babies showed delayed respiration but ultimately breathed spontaneously, while 15 per cent required resuscitation. Torpin [4] recorded the incidence of asphyxia requiring resuscitation as 7 to 10 per cent. The incidence of resuscitation in our clinic is 5 to 10 per cent.

The decision whether or not a sleepy baby requires resuscitation is difficult. Often it is a matter of one's individual judgment, which probably accounts for the wide discrepancies in incidence reported in the literature.

3. Cole, W. C. C.: Asphyxia During Delivery and Immediately Postpartum. J. Pediat. **19**:258-273, 1941.

4. Torpin, R.: The Care of the Fetus During Labor, J. A. M. A. **124**:343-351 (Feb. 5) 1944.

Cole,[3] together with Russ and Strong,[5] expressed the belief that for practical purposes a newborn infant should be considered asphyxiated when breathing does not take place within thirty seconds. They pointed out that about four minutes is the maximum time the brain cells can survive without oxygen and that irreversible changes may occur in less than one minute.

In the interval between birth of the head and the first inspiration, the infant's mouth and nose and the posterior portion of the pharynx should be cleared by gentle suction.

The condition of the asphyxiated newborn infant is never static. If mild asphyxia is present at birth, the baby either recovers rapidly or proceeds with like speed through the moderate and severe stages of asphyxia to death. This latter possibility is always in mind when a mildly asphyxiated baby is being treated. Whatever fluid may be present in the air passages is removed by postural drainage, gentle milking of the trachea and suction. The cord is allowed to continue pulsating so as to pick up as much of the added oxygen being administered to the mother as possible.

If the baby passes into the stage of moderate asphyxia or if it is born at this stage, the cord is allowed to pulsate so long as it is felt that added oxygen is being delivered to the infant. Litchfield[6] recommended that prior to cutting the cord the umbilical vein be injected with 3.0 mg. (1/20 grain) of alphalobeline hydrochloride and stripped to just short of the halfway mark. A clamp is applied here and the cord cut. Thus, the drug is not in the general circulation but readily available for use if needed.

For subsequent efforts at resuscitation, it is imperative that the baby be kept warm, either in a warm blanket or in a body temperature bath.

As to the next step, all agree that the air passages should be cleared of foreign material. The most efficient method of accomplishing this should be by direct laryngoscopy and tracheal suction, provided trained personnel skilled in this procedure are available. Lacking readily available trained personnel, we at our clinic rely on postural drainage with gentle milking of the trachea, suction of the mouth and nasopharynx and tracheal suction through a rubber catheter introduced under digital direction.

The baby's fundamental need is for oxygen. Since the lungs have never expanded, artificial resuscitation not only is useless but may be

5. Russ, J. D., and Strong, R. A.: Asphyxia of the Newborn Infant, Am. J. Obst. & Gynec. **51**:643-651, 1946.

6. Litchfield, H. R.: Asphyxia Neonatorum, J. Pediat. **26**:279-286, 1945.

harmful. Wilson, Torrey and Johnson [7] showed that the atelectatic lung cannot be opened by gases under pressure in the trachea alone.

Smith [8] reported that the atelectatic lung caused by intrauterine asphyxia could be expanded by 30 cm. of water negative pressure but that emphysematous blebs had already begun to develop at 19 cm. of pressure. Our experience with the Drinker infant respirator for babies who had not breathed was the same as that of Litchfield [6]—it was of no value.

A small amount of oxygen can be absorbed from the skin and mucous membranes. Thus the infant may derive some slight benefit from being placed in an environment of oxygen. The trachea can be filled with oxygen under slight pressure by direct intubation, by a face mask or by mouth to mouth insufflation. It is important that as high a concentration of oxygen as possible be available for the baby's first gasp when and if it comes. That first gasp may allow enough oxygen to reach the higher respiratory centers to "open the door to life."

In this desperate effort to provide oxygen through the first gasping respiration I believe alphalobeline hydrochloride has a definite place in the obstetrician's armamentarium. Many authors, Cole [3] and Russ and Strong [5] among them, were of the opinion that no drug is of value in stimulating respiration. My personal experience agrees with that of Litchfield.[6] I have seen 4 or 5 babies in the final stages of asphyxia in whom the injection of the drug into either the heart or the anterior longitudinal sinus was followed in ten or fifteen seconds by a convulsive inspiratory gasp, succeeded by at least temporary spontaneous respiration.

Once respiration has been initiated, the baby must be kept warm and placed in an atmosphere of 50 to 60 per cent oxygen. He should be in a nursery where he can be kept under constant observation and given symptomatic treatment.

ATELECTASIS IN INFANTS DELIVERED BY CESAREAN SECTION

In 1934, I reported a mortality rate of 54 per cent for infants weighing 5 pounds (2,268 Gm.) or less delivered by cesarean section as compared with a rate of 15 per cent for those delivered by low forceps with episiotomy. I suggested that the high mortality might be the result of intrauterine asphyxia secondary to the type of anes-

7. Wilson, R. A.; Torrey, M. A., and Johnson, K. S.: Initiation of Respiration in Asphyxia Neonatorum, Surg., Gynec. & Obst. **65**:601-622, 1937. Wilson, R. A., and Torrey, M. A.: Effects of Alpha-Lobelin on Respiration, Am. J. Surg. **23**: 426-437, 1934.

8. Smith, C. A.: Round Table Discussion on Neonatal Asphyxia, J. Pediat. **19**:258-273, 1941.

thesia used. After this suggestion was made, methods of anesthesia were instituted minimizing the danger of fetal asphyxia, with the result that in 1940 I reported two and one-half years' experience with 24 infants in this weight group delivered by cesarean section with a mortality rate of 16.5 per cent.[8a]

I have long observed that certain normal full term infants delivered by cesarean section did poorly and developed unexplained, serious atelectasis. I have been at loss to explain this fact and have assumed that delivery through the birth canal must somehow condition the child for extrauterine life.

Russ and Strong [9] observed that many cesarean sections were performed with the thought that the procedure would protect the infant but that this conclusion is far from true. They found the average infant death rate in delivery by cesarean section to be 9 to 10 per cent. These infants usually had breathed spontaneously or within a few minutes of birth without receiving large doses of stimulants. They seemed to be in good condition for several hours (many had a slight grunting respiration), then respiratory distress with cyanosis developed. The attacks often recurred and resulted in death. At autopsy the alveoli were observed to be expanded but covered with a semimembrane of amniotic fluid, meconium, lanugo, blood and detritus.

The authors demonstrated that direct tracheal aspiration following normal delivery from below produces 1 or 2 cc. of mucoid material, while in aspiration following cesarean section an average of 3 to 7 cc., and frequently much more, of thick, mucoid material is aspirated. They strongly recommended that after delivery by cesarean section every infant be immediately aspirated by intratracheal catheterization. They reported that in their clinic this procedure reduced the death rate following cesarean delivery from 10 to 2 per cent.

Russ and Strong [5] reported that 85 to 95 per cent of the infants they delivered by cesarean section were asphyxiated at birth. Presumably, intrauterine asphyxia is the reason these babies aspirate amniotic fluid. Possibly the same attention to anesthesia and analgesia that reduced our premature infant mortality may reduce the amounts of asphyxia and aspiration in the full term babies delivered by section. Bloxsam's [10] observations lend weight to the latter suggestion. Elim-

8a. Clifford, S. H.: Reduction of the Premature Infant Mortality, J. Pediat. **5**:139-155, 1934; Asphyxia of the Fetus and the Newborn Infant, Am. J. Obst. & Gynec. **39**:388-394, 1940.

9. Russ, J. D., and Strong, R. A.: Asphyxia of the Newborn, bol. méd. d. Hosp. inf., Mexico **5**:27, 1948. Footnote 5.

10. Bloxsam, A.: The Difficulty in Beginning Respiration Seen in Infants Delivered by Cesarean Section, J. Pediat. **20**:215-222, 1942.

inating premature infants and those exposed to definite intrauterine asphyxia, he reported 32 per cent of those delivered by cesarean section requiring resuscitation at birth as opposed to 18 per cent after normal delivery. He pointed out the dangerous effects of analgesics, particularly morphine and its derivatives, and of some anesthetics on the newborn infant delivered by cesarean section.

CLINICAL PICTURE OF NEONATAL ASPHYXIA

The infant who has anoxia may appear to be in fair condition for several hours following mild asphyxia at birth except for slight grunting respiration and possibly some cyanosis of the extremities. Other infants may show severe respiratory distress from birth, with labored, grunting breathing, dilatation of the alae nasi and pronounced retraction of the costal margins. They are subject to periods of apnea and to varying degrees of cyanosis; their cries are feeble; the reflexes are absent, and muscles are hypotonic. The majority show petechial hemorrhages and subcutaneous ecchymoses. There may be evidence of gross bleeding; the infant may vomit blood or pass blood by rectum. There may be bleeding into the cerebrospinal fluid. They may show the development of localized or generalized edema, and excessive fluid may accumulate in the subarachnoid space or in any of the body cavities. Injury to the central nervous system may be evidenced by convulsions, coma, irregular respirations or periods of apnea.

DIFFERENTIAL DIAGNOSIS OF NEONATAL CYANOSIS

In the differential diagnosis of cyanosis in the newborn the following conditions must be considered:

I. Respiratory system
  A. Pulmonary atelectasis
    1. Normal resistance to expansion [11] due to cohesion of moist surfaces, together with
      a. Injury to respiratory center
      b. Imperfectly developed thoracic mechanism
      c. Bronchial obstruction due to aspiration of contents of amniotic sac, mucus or blood
    2. Increased turgor of pulmonary tissue itself [12] due to the congestion, edema and hemorrhage associated with asphyxia
  B. Infection
  C. Congenital defects
    1. Agenesis of the lung
    2. Atresia of bronchi

11. Wilson, J. L., and Farber, S.: Pathogenesis of Atelectasis of the Newborn, Am. J. Dis. Child. **46**:590-603 (Sept.) 1933.

12. Clifford, S. H.: The Effects of Asphyxia on the Newborn Infant, J. Pediat. **18**:567-578, 1941.

3. Tracheoesophageal fistula
4. Diaphragmatic hernia

D. Extrinsic pressure on trachea or bronchi

II. Central nervous system
A. Injury to respiratory center

III. Circulatory system
A. Congenital heart disease
B. Polycythemia
C. Methemoglobinemia
D. Sulfhemoglobinemia
E. Dehydration

IV. Adrenal hemorrhage
(Waterhouse-Friderichsen syndrome)

TREATMENT OF INFANTS WITH NEONATAL ASPHYXIA

Atelectasis.—All infants who have been exposed to even a short period of anoxia should be placed in an atmosphere of 50 to 60 per cent oxygen for a period of observation of at least twelve to twenty-four hours.

Suction equipment should be constantly at hand and used when needed. The nursing staff in our hospital is given blanket permission to aspirate the oral, nasal and posterior pharyngeal cavities whenever indicated. On the rare occasions in our nursery when direct laryngoscopic examination and bronchoscopic drainage are thought advisable, the procedures are carried out by a skilled consultant.

Babies with varying degrees of atelectasis make up more than half of our morbidity. Fortunately, the recovery rate is more than 80 per cent with the use of conservative measures. The treatment consists of constant administration of oxygen, use of suction when necessary and allowance of nothing by mouth for at least forty-eight hours. It is a striking fact that both clinical and roentgenographic improvement takes place sharply and dramatically between the third and fourth day. At this time, the vernix membrane, as well as the pulmonary congestion, edema and hemorrhage, is largely absorbed and the alveoli begin to function normally.

The use of positive pressure methods for expanding this type of atelectatic lung is both futile and dangerous. Under positive pressure the air will take the path of least resistance, converting the few functioning alveoli, on which the infant's life is depending, into emphysematous blebs that may further rupture and produce pneumothorax.

The use of bronchoscopic drainage in the treatment of neonatal atelectasis has been suggested. In the opinion of Woodward and Waddell [13] the procedure is seldom indicated, but on rare occasions

13. Woodward, F. D., and Waddell, W. W., Jr.: Bronchoscopy in the Newborn Infant, J. Pediat. **23**:79-86, 1943.

it may be saving of life when body secretions obstruct the bronchi. They expressed the belief that in skilful hands bronchoscopy of newborn infants is a safe procedure.

Greenberg [14] stated his belief that management of asphyxia of the newborn infant frequently necessitates direct visualization of the larynx. He recognized that treatment of newborn infants with the laryngoscope has always been a difficult problem because of (1) the need of special skill, (2) the necessity of absolute prerequisite indication for its use and (3) fear of increasing trauma and consequent dangers especially present in premature and newborn infants. These difficulties have relegated laryngoscopy to especially trained otolaryngologists or anesthetists. The disadvantage of this solution is that frequently the time spent in obtaining such skilled consultants has been an unfavorable deciding factor in the life of the patient. Greenberg [14] perfected a modification of Flagg's [1] laryngoscope which he implied can be used safely by obstetricians and pediatricians with a minimum of experience. He described 3 dramatic instances of neonatal atelectasis: 1 due to aspiration of milk, 1 to aspiration of meconium and 1 due to congenital laryngeal stenosis, each of which was relieved through the use of his instrument.

The paper by Woodward and Waddell [13] stimulated the interest of pediatricians in Los Angeles, with the result that House and Owens [15] were requested to perform bronchoscopic examinations on 23 patients (19 of them premature infants) with atelectasis who had not responded to conservative therapy. They discovered it imperative prior to bronchoscopy to rule out the various pathologic entities due to bronchial obstruction that may resemble atelectasis. These include asphyxia, congenital disease of the heart and blood vessels, congenital cystic lung, cerebral trauma, blood dyscrasias, pulmonary infection, diaphragmatic hernia and congenital fetal atelectasis. In each of their cases some secretions were aspirated from the bronchial tree, but in only 1 was a definite thick, stringy plug of exudate removed from a single bronchus. The improvement was not immediate after treatment with the bronchoscope; complete relief took from six to eight hours. It is difficult to decide of how much value bronchoscopy really was in the series of House and Owens,[15] since individual case histories were not submitted. It is of real importance that they were able to treat 19 premature and 4 full term infants with the bronchoscope with little, if any, shock to the babies and without the appearance of laryngeal edema secondary to the procedure.

14. Greenberg, L. J.: The Greenberg Modification of the Flagg Laryngoscope: Its Use in Asphyxia Neonatorum, J. Pediat. **27**:602-605, 1945.

15. House, H. P., and Owens, H.: Atelectasis of the Newborn: Treatment by Bronchoscopic Drainage, J. Pediat. **28**:207-209, 1946.

My personal conclusions as to the role of direct tracheal or bronchial visualization and aspiration in the newborn period may be summarized as follows:

I. In resuscitation

A. Vaginal deliveries

In all types of asphyxia immediate, efficient, direct aspiration before respiration starts should be recommended, provided proper equipment and a trained operator are ready and waiting to perform this procedure.

If this ideal setup is lacking, immediate postural drainage, suction of the nasal, oral and pharyngeal spaces and intratracheal suction with a catheter introduced under digital guidance in moderate or severe asphyxia should be instituted—all before respiration starts if possible. Once respiration has begun, tracheal and bronchial secretions have been drawn too deep into the lungs to be aspirated even by direct procedures.

B. In deliveries by cesarean section

A properly equipped and trained operator should, on the evidence of Russ and Strong,[5] be part of every cesarean section team so that a direct tracheal aspiration may be performed on the infant the instant of birth.

II. In the newborn period

A. Diffuse atelectasis of the newborn cannot be helped by tracheal or bronchial drainage. Many years of autopsy observation showed no evidence that obstruction material was present that could have been removed by suction. The pathologic lesions are in the alveolar ducts, alveoli and pulmonary tissue.

B. Bronchoscopic examination by a consultant otolaryngologist is indicated when physical examination and roentgenograms reveal a localized obstruction.

C. Instant direct tracheal and bronchoscopic drainage is indicated in sudden asphyxia following an accident such as the aspiration of milk.

D. Direct examination by a consultant otolaryngologist is necessary when a developmental abnormality of the larynx, trachea, bronchi or lung is suspected.

It is evident that emergencies arise at birth and in the newborn period which are too acute to permit calling a consultant. Some members of the anesthetic and resident obstetric staff should be trained in the use of the Greenberg laryngoscope and the technic of tracheal aspiration.

Edema.—Anoxia almost always produces some degree of edema in the affected newborn. This edema may approach generalized anasarca; it may be observed as pitting edema in the extremities; it may become evident as cerebral edema, or it may be responsible for a great accumulation of clear fluid in the subarachnoid space. As pulmonary edema, it may be the chief factor in the atelectatic picture.

To summarize the treatment of neonatal asphyxia: the first rule is to clear the airways; the second is to provide oxygen. The third rule is to keep the baby warm, and the fourth rule is to withhold the administration of all food and fluids in the presence of edema. To offer added fluid to an already waterlogged baby may increase the existing pulmonary or cerebral edema to fatal proportions.

TREATMENT OF CEREBRAL SYMPTOMS

Asphyxia may cause cerebral edema and an increase in cerebrospinal fluid, or it may produce petechial or larger hemorrhages into the brain substance and bleeding into the subarachnoid space. These changes may produce any variety of cerebral symptoms, such as unconsciousness, convulsions, interference with the respiratory center, apnea and cyanosis. Eventually, the anterior fontanel may bulge, but the condition can usually be detected before this stage through palpating an increased intracranial tension in the fontanel.

When intracranial disease is suspected, a lumbar puncture is indicated. Such a procedure is both diagnostic and therapeutic. In the case of edema, clear fluid is obtained in excessive amounts under pressure. Some cases will show xanthochromic fluid, with or without small amounts of microscopic old blood, usually in excessive quantities. This indicates the original bleeding into the spinal fluid took place long enough before to allow hemolysis to take place. In many cases blood-stained fluid will be removed. If the blood present is large in amount, usually a traumatic factor coupled with the anoxic bleeding is indicated. If the number of red cells are few enough to count without dilution in the blood-counting chamber, the injury is interpreted as probably the result of anoxic bleeding alone.

In all cases 5 or 10 cc. of fluid should be slowly removed and the procedure repeated every twelve to twenty-four hours, as clinically indicated, until the fluid is nearly normal. I believe that this method of treatment gives symptomatic relief, minimizes intracranial injury from pressure and helps to prevent the later development of hydrocephalus. It has been used for many years, and I have yet to see an instance in which I thought the withdrawal of fluid had resulted in increased intracranial bleeding.

SUMMARY AND CONCLUSIONS

The presence of golden yellow vernix at birth identifies a baby who has had anoxia days or weeks before delivery. The probable cause of this anoxia is placental disease. Some of these infants have erythroblastosis, but the bulk of them do not. A large number show symptoms attributable to anoxia: asyphyxia, atelectasis, cyanosis convulsions, hypertonia and hypotonia, petechial and gastrointestinal bleeding.

The remaining infants showing fetal anoxia at birth had their anoxic injury either during the delivery process or as the result of a number of causes that become evident after birth. Among these causes are injury of the respiratory center due to anoxia or trauma or both, tracheal or bronchial obstruction and congenital malformation of the cardiovascular or respiratory system.

The condition of babies who do not breathe within thirty seconds of birth is diagnosed as mild, moderate or severe asphyxia after a modification of Flagg's classification. The technic of resuscitating the newborn consists of (1) clearing the airways, (2) providing oxygen under slightly positive pressure, (3) keeping the baby warm, (4) administering a respiratory stimulant if needed and if one finds them useful and (5) constant observation and symptomatic treatment.

Supposedly normal infants delivered by cesarean section experience a mysteriously high mortality and morbidity rate. Severe atelectasis develops in many of them. This may be due in part to intrauterine asphyxia and aspiration related to the type of maternal analgesia and anesthesia. Russ and Strong [5] indicated that some of the bad after-effects of cesarean section can be prevented or minimized by immediate direct tracheal suction of the large amount of mucus and fluid aspirated by the infants.

The cyanosis caused by neonatal asphyxia must be differentiated from that due to congenital heart disease and to intracranial injury. Cyanosis may also result from pulmonary infection or infection involving the respiratory center. Agenesis of the lung, bronchial atresia, tracheoesophageal fistulas, diaphragmatic hernia, polycythemia, dehydration, methemoglobinemia, sulfhemoglobinemia and adrenal hemorrhage constitute rarer conditions that may produce cyanosis.

The conservative treatment of atelectasis consists in keeping the baby warm and leaving him alone in an atmosphere of 50 to 60 per cent oxygen. Suction is performed as needed to remove obvious mucus. Nothing is given by mouth for two or three days; this is particularly important if edema is present. Under this regimen dramatic improvement usually takes place, both clinically and roentgenographically, between the third and fourth day. Should atelectasis continue beyond this time, prophylactic sulfadiazine and penicillin is given and a fresh search for other diagnostic possibilities is instituted. Cerebral symptoms are investigated and treated by lumbar puncture and drainage.

PATHOLOGIC CONDITIONS RESULTING IN FETAL ANOXIA AND CYANOSIS OF THE NEWBORN

W. W. ZUELZER, M.D.
DETROIT

ANOXIA is a concept of pathologic physiology. Strictly speaking, from the standpoint of pathologic anatomy lesions cannot be ascribed to anoxia because the term, as applied to cells and tissues, has not been sharply defined. A workable definition of tissue anoxia would require knowledge not only of the oxygen content and tension of the blood but of physiologic conditions inside the various tissue cells, their rate of oxygen utilization, their metabolic activity, their state of function, their adaptability to oxygen want and their absolute minimum requirements. There is reason to believe that these factors may vary from cell to cell, from tissue to tissue and from time to time. Moreover, the degree and the duration of oxygen deprivation are bound to influence the effects of anoxia. Thus, anoxia appears to be a relative state, and it is difficult to know at which point and in what circumstances the condition may produce organic residues. The difficulties are especially great in the case of the fetus and newborn infant in view of the evidence that cellular oxygen requirements in utero and at birth may change rapidly and differ from those in later life.

Failure to consider all these factors has given rise to assumptions about the pathologic effects of anoxia which are as yet unproved and perhaps impossible to prove. I shall, therefore, confine my remarks to the pathologic changes in conditions characterized by respiratory distress and failure in the fetus and newborn child.

Further reservations are necessary. Respiratory difficulties may have their basis in structural changes in the organs of respiration or circulation, but often the causes are purely functional and cannot be grasped with morphologic methods. The effects of oxygen deprivation on the tissues are also largely functional. The organic lesions commonly attributed to anoxemia are stereotyped and give no clue to the nature of the original injury. Such lesions, however, may in turn further impair physiologic mechanisms. The pathologist who examines newborn infants dead of respiratory failure cannot always distinguish between cause and effect and must depend for the interpretation of his observations largely on the history of preceding events. Since crucial events are likely to occur in utero and to involve pri-

marily structures outside the fetal body proper, the information is rarely complete and conclusions are often drawn by inference.

It must also be kept in mind that anatomic conditions change rapidly at birth and that a condition which may be normal at one moment may be pathologic the next. Since the lungs even normally do not expand completely with the first breath, the diagnosis of their state post mortem becomes a quantitative judgment influenced by the time factor. Finally, the postmortem observations may be modified by such measures as artificial respiration.

It is clear then that the pathologic examination cannot by itself afford an insight into the mechanism of respiratory failure in the newborn, although it forms a valuable adjunct to other methods of study, if the limitations of the method are kept in mind.

MECHANISMS OF ANOXIA

Dr. Clement A. Smith, in a preceding paper, pointed out that anoxia in the newborn period is likely to be of the anoxia type, produced in one of two ways: either by interference with oxygenation of the blood itself or by the presence of circulatory shunts which prevent oxygenated blood from reaching the tissues. This discussion is chiefly concerned with the first of these mechanisms, since malformations of the circulatory system form a separate chapter.

INTRAUTERINE ASPHYXIA

The fetal organ of respiration is the placenta, and fetal oxygenation depends on three factors: (1) adequate supply of oxygen in maternal blood; (2) intact placental structure and circulation, and (3) intact pathways for blood from placenta to fetus.

The common conditions interfering with fetal oxygenation have their site of action outside the fetal body and will therefore be mentioned only briefly as: (1) maternal disease capable of producing anoxemia; (2) placental disease, placental separation, placenta previa and prolonged uterine contractions, and (3) compression of the cord.

The effect of each of these conditions on the fetus will be the same, depending on duration and severity of the primary cause. Acute severe anoxemia leads to fetal death unless relieved. If the oxygen supply is restored in time, the fetus may continue to live in utero, although in the meantime changes may have occurred which make an extrauterine existence precarious or impossible.

First are the changes connected with asphyxia in general: severe vascular congestion, petechial hemorrhage and edema. As Dr. Clifford pointed out, these changes may interfere with proper functioning of many organs at the crucial time of birth and, in particular, may render

expansion of the lungs difficult at that time because of the increased turgidity and wetness of the alveolar walls and the extravasation of blood or edema fluid in the lumens.

In addition, a complication peculiar to fetal life occurs when the stimulation of the respiratory center early during asphyxia produces strong respiratory movements which tend to draw large amounts of amniotic fluid into the lungs. The presence of the fluid does not matter greatly so long as the fetus remains in utero, as the lungs can have no true respiratory function at that time. After birth, however, the fluid causes obstruction and atelectasis, even if the respiratory center has by that time recovered its function. Such infants may be born seemingly in good condition, only to die later of progressive obstruction.

A further effect of intrauterine asphyxia is the functional depression of the respiratory center. If the infant is born while the center is unresponsive to the normal stimuli, failure to breathe will result.

From this point on it seems best to make an artificial distinction and to consider the respiratory center and the respiratory tract separately. In doing so, it must be kept firmly in mind, however, that the two systems are closely linked. Under pathologic conditions, their interdependence invariably produces a vicious circle, the starting point of which cannot always be determined. A damaged respiratory center may cause impairment of pulmonary ventilation, but poor air exchange in the lungs will in turn asphyxiate the nerve cells of the center.

CHANGES AFFECTING THE RESPIRATORY CENTER

The respiratory center is a term again with more physiologic than anatomic meaning. Its pathologic changes are not often demonstrable with the dissecting knife or the microscope. Immaturity is perhaps the commonest cause of central failure, and it is difficult to appraise by anatomic means. The general development of the fetus gives only a crude index of function, and there is no morphologic method which would indicate the exact degree of immaturity incompatible with life.

Likewise, the functional depression of the center caused by analgesic or anesthetic drugs given to the mother is beyond anatomic recognition.

Asphyxia itself due to interference with placental respiration has already been mentioned as a cause of depression of the respiratory center. The brain of infants with this condition may show congestion, edema and petechial hemorrhage, but it is difficult to distinguish such lesions from those produced by local mechanical trauma, due to compression and distortion of the head, which undoubtedly play a part in prolonged and difficult deliveries. The subsequent clinical significance of such lesions has not been established. Minute areas of softening, glial scar formation and hemosiderosis are often observed in the brain of infants.

However, proof that these lesions are due to anoxia as such is lacking; it is equally possible that they may be caused by physical trauma.

For gross hemorrhage at birth the weight of evidence certainly suggests mechanical traumatic origin. The trauma, however, is not necessarily the result of obstetric procedures or even of unduly difficult delivery. This is especially true in premature infants in whom hemorrhage into the ventricles, the substance of the brain or the subarachnoid space is often seen after seemingly easy delivery. The softness of the skull and the fragility of the blood vessels are held responsible for the susceptibility of these infants to intracranial hemorrhage. Perhaps the extreme softness of the immature brain itself is a contributory factor.

In the full term infant gross hemorrhage is usually, though not always, associated with a history of prolonged and difficult labor or obstetric procedures. The origin can be definitely labeled traumatic if other signs of mechanical injury, such as tears in falx, tentorium or cerebral veins, or fractures of the skull, are present. The stresses to which the skull is subject produce stretching of the delicate veins coursing from the relatively movable brain to the fixed dural structures, especially the vein of Galen and the superior cerebral veins. Even when rupture or tearing does not occur, temporary occlusion may lead to softening or hemorrhage in the drainage area and sometimes to thrombosis. Hemorrhage need not involve the area of the respiratory center directly but may exert its effects by increased pressure, especially when the posterior fossa is involved.

Inflammatory conditions of the central nervous system rarely cause respiratory difficulties at birth but may do so later in the newborn period, when cyanosis or dyspnea may be the first sign of meningitis, usually secondary to Eschenchia coli septicemia.

CHANGES AFFECTING THE RESPIRATORY TRACT

The respiratory tract must be in condition for instantaneous function at birth. The air passages must be patent; the alveoli must be capable of expanding; space must be available in the thorax for expansion of the lungs; the thoracic cage must be sufficiently rigid to permit negative pressure to develop, and the diaphragm must be able to move downward.

Obstruction of the air passages from anatomic causes is rare. Compression of the trachea by the thymus is often mentioned, but it too must be rare. In almost 2,000 autopsies on infants and children, this complication has not been seen in our laboratory. Mucus or amniotic fluid obstructing the airways is probably the commonest cause of respiratory difficulty at birth. The obstructing material becomes the concern

of the pathologist only when it is not removed but allowed to be drawn farther into the lungs either by the infant's own efforts or by artificial respiration.

Aspiration may, of course, have taken place in utero, as was mentioned before. No complete agreement about the state of the lung before the first breath has yet been reached, and some authors maintain that amniotic fluid is normally present in the alveoli at birth. Certainly, small amounts can be demonstrated in the majority of all newborn infants, but there is no reasonable doubt that the presence of amniotic fluid in large amounts is a pathologic condition and that it indicates asphyxia in utero or during labor. Here again the diagnosis is quantitative.

Amniotic fluid is recognized by the presence of vernix caseosa and keratinized epithelial cells derived from fetal skin. As air enters the lung, the aspirated vernix is pushed against the walls of the bronchioles and alveoli, compressed and formed into dense membranes which interfere with exchange of gases.

Forced spontaneous or artificial respiration may distend such membrane-lined air spaces but cannot overcome the difficulty. Rupture of alveolar walls may result.

The air entering the interstices of the lung finds its way to the pleura, or the subpleural alveoli may rupture directly. Interstitial pulmonary emphysema and pneumothorax can thus be produced, which further increase respiratory difficulties.

The aspirated material may be infected, especially if the membranes ruptured early, permitting bacterial invasion of the amniotic fluid. The development of pneumonia in those circumstances is almost inevitable, though it may be difficult to recognize. Pneumonia in the newborn is by no means rare and is usually explained in this manner. Abscesses may form and rupture into the pleura, causing pyopneumothorax.

Aspiration of secretion from the nasopharynx and of feedings from a blind esophageal pouch is responsible for respiratory distress in congenital atresia of the esophagus, a not uncommon malformation.

The structure of the lung itself is, of course, of the greatest importance for its function. Here again the premature infant is handicapped. The lung develops as a tubuloalveolar gland growing into a solid mesenchymal stroma. At first, the alveoli are solidly lined with epithelium and widely separated by abundant connective tissue. The blood vessels are relatively few and have not yet entered into close relation with the alveoli. The latter increase in number at the expense of the stroma, which disappears in the process except for peribronchial, perivascular and interlobular tissue. The capillaries proliferate, surround the alveoli and elongate, pushing inward between the epithelial lining cells. Thus, the continuity of the epithelium is disrupted; the capillaries

come in contact with the potential air space, and their tortuosity provides the slack necessary for expansion. When the fully developed lung expands, the festoon-like outline of the alveoli becomes smooth; the remaining epithelial cells flatten out and disappear, and the exchange of gas can proceed without impairment.

The immature lung is not yet functionally adapted. It is relatively rigid because of its abundant connective tissue which prevents expansion of the alveoli. In inspiration bronchi and alveolar ducts are filled with air but the alveoli themselves do not open. Such oxygen as does find its way into the terminal air spaces must pass through the thickness of a solid cuboidal epithelium and through connective tissue to reach the capillaries. For this most primitive state of the premature lung, which is nevertheless compatible with life, at least for a short time, Farber proposed the term anectatos to indicate the distinction between this condition and atelectasis, i.e., failure of potentially expansible lung to distend. The transition to the mature state is a gradual process, and respiratory difficulties caused by structural immaturity become less of a problem after the eighth month of gestation.

Still another handicap in the respiration of the premature infant arises from the softness of the thorax. The downward motion of the diaphragm acting on a pliable instead of a fixed, rigid thorax causes the chest wall to cave in under atmospheric pressure. This inspiratory retraction, which is familiar to the pediatrician, counteracts the establishment of negative pressure needed for expansion of the lung.

Atelectasis in the newborn is the result, not the cause, of failure to breathe. Although it may be the only anatomic irregularity it should not be considered as a diagnosis capable of explaining death.

Primary atelectasis, that is, failure of the alveoli to expand, can be recognized by the persistence of cuboidal epithelium in the lining of the air spaces and by the shape of the alveoli, which differs from the cleftlike appearance of secondarily collapsed alveoli from which air has been resorbed.

As Wilson and Farber showed, the initial effort needed to expand the alveoli from their fetal state is greater than that required to maintain a tidal flow of air in the once expanded lung. The cohesion of the moist surfaces must be overcome, and this requires relatively large negative pressures. Central respiratory failure, prematurity, bronchial obstruction, edema, hemorrhage, splinting from interstitial emphysema and poor development of the thorax are the chief reasons for the infant's inability to overcome the factor of cohesion.

It has been mentioned that artificial respiration cannot force the atelectatic alveoli to open. Such attempts result in distention of proximal structures and may cause emphysema and pneumothorax.

Massive pulmonary hemorrhage rarely if ever causes respiratory difficulties at the time of birth but accounts for many of the deaths due to respiratory difficulties in the next few days. Hypoprothrombinemia may be a major factor but does not explain pulmonary hemorrhage in many instances.

Inability of the lung to expand may be the result of abnormal processes which take up space within the thorax. This may be one of the effects of a large heart. Occasionally, a diaphragmatic hernia is large enough to cause respiratory distress at birth. Abdominal distention from various causes frequently gives rise to cyanosis and dyspnea by preventing the excursion of the diaphragm.

Congenital heart disease in relation to cyanosis of the newborn is beyond the scope of this discussion but should be mentioned because the symptoms may resemble those of respiratory failure. This is true particularly in two types of malformations: those in which an insufficient amount of blood reaches the lung, as, for example, in pulmonary atresia, and those in which the aorta is so underdeveloped that the ductus arteriosus pumps most of the blood into the systemic circulation, as in coarctation of the aorta.

5224 St. Antoine Street (2).

DISCUSSION

Panel Question.—What is the effect on the baby of administering oxygen to the mother during the terminal stage of labor?

Dr. N. J. Eastman, Baltimore: Of course, if a mother has any condition which leads to stagnant anoxia on her part, such as pneumonia, cardiac failure, or anoxia consequent on anesthesia induced with nitrous oxide, it is imperative to give oxygen to that mother in the course of labor. However, in a woman who does not have anoxia, whose blood is normally saturated with oxygen, the problem is different. I am referring now to the case in which the mother's respiratory apparatus is satisfactory, but in which the baby, for one reason or another, is in distress and apparently has anoxia. In that instance, I should recommend administration to the mother of oxygen. It does no harm and may possibly do good. My skepticism about its efficacy in improving the fetal oxygen content is based on the fact that the mother's arterial blood is already 97 per cent saturated with oxygen and the best one could hope for in administering oxygen to her would be to raise the saturation to, perhaps, 99 per cent.

Because of the structure of the oxygen association curve, this 2 or 3 per cent increase in saturated arterial blood would increase the oxygen tension so minimally that I should question whether the blood corpuscles would be in any better position to help out the baby than they were before.

Dr. Stewart H. Clifford, Boston: I notice Dr. Eastman said nothing about delaying the normal birth of the head as an obstetric cause of anoxemia in the baby.

Dr. N. J. Eastman, Baltimore: I think that holding back the head used to be a more frequent practice in obstetrics than it is today. For instance, nurses

used to hold the thighs together or keep the baby from being born until the physician arrived and that sort of thing. I can only regard that practice as reprehensible, as possibly damaging to the infant's head, as submitting the infant to continued anoxia perhaps from continuation of uterine contractions, and I should think that in modern obstetrics it would be looked on generally with disfavor.

Panel Question.—What time may elapse before brain tissue is permanently damaged by anoxia?

DR. WOLF ZUELZER, Detroit: That question is extremely difficult to answer, partly because pathologic demonstration of irreversible brain damage is at the best a crude tool and, in order for those changes to develop, time is needed so that one does not see them until perhaps weeks or months later. The second reason for hedging on that question is that the fetus and perhaps the newborn animal may tolerate anoxia to a much greater degree or for a greater period of time than the same animal, or another animal of the same type, several days later or certainly in adult life, so that I think it is difficult to give a conclusive answer for that on pathologic grounds.

The answer is usually stated in terms of adult tissue. I think this approach simply does not apply to the fetus. It also will depend a great deal on the efficacy of the circulation at that time, and one of the slides which I showed brings out the fact that Dr. Eastman stressed, that there is a certain amount of stagnant anoxia which one may not be able to evaluate but the phases of it are seen later.

DR. STEWART H. CLIFFORD, Boston: There has been experimentation in fetal animals, too. The fetus can tolerate lack of oxygen for a period of approximately three minutes.

DR. WOLF ZUELZER, Detroit: Longer than that, I think. In puppies it goes up to thirty minutes.

DR. N. J. EASTMAN, Baltimore: Most apneic babies, I think, are overtreated rather than undertreated. For instance, I view with a great concern the references to direct visualization of the larynx, to bronchoscopic drainage and all those procedures which entail trauma to the baby and to the larynx with great likelihood of subsequent laryngeal edema.

The fact that trauma can be done to the epiglottis and the larynx indicates that physicians are to be cautious, careful and gentle in their manipulations. For instance, the instrument used chiefly for aspirating the posterior portion of the pharynx in a newborn infant is an ordinary rubber ear syringe with which little harm can be done, and it is quite efficacious.

Panel Question.—What is the advantage of the practice of milking the cord after cutting it?

DR. N. J. EASTMAN, Baltimore: It has never been my practice to milk the cord after cutting it. The objective was supposed to be to give the baby more blood. Several studies attest the fact that if one does not cut the cord immediately after birth but allows it to continue pulsating the average baby receives about 90 cc. of blood from the placenta within the first three minutes of life. About 50 cc. of blood of this 90 cc. is transported in the first minute of life. Recalling that the total blood volume of the newborn infant of average size is approximately 400 cc., one can understand what a tremendous relative amount of blood this is to the infant; for that reason, it seems to me that the present day practice of cutting the cord immediately is somewhat undesirable.

Of course it has to be done now and then, but I like to wait for a minute or two and let the baby get all the blood he possibly can. As for milking the cord, the amount of blood obtainable from the cord after it is cut is small in comparison to what may be obtained from the placenta. For that and other reasons, which it is not necessary to go into now, I have never looked on the procedure with much favor.

DR. STEWART H. CLIFFORD, Boston: I imagine the question means cutting the cord immediately and then milking the blood that is in the cord without waiting for the cessation of pulsation.

DR. N. J. EASTMAN, Baltimore: There is no reason to milk the cord. If the baby is put on the scale and the increase in weight over the minimum is observed, this will be seen. As I mentioned in my paper, in the premature babies, in whom anemia is so likely to develop, I find it important to allow the cord to continue to pulsate for a minute or two. The baby need not be exposed; it can be covered and kept warm, but this amount of blood is a huge transfusion for the anemic baby.

Panel Question.—Is there any objection to having the oxygen administered to a premature baby go through ice?

DR. STEWART H. CLIFFORD, Boston: One certainly does not want to chill the baby with iced oxygen. I think the humidification of the oxygen that the baby has from the dry oxygen tank is an important advantage.

It ought to be put through some type of solution, but I cannot say whether the baby is chilled, because my colleague and I do not use ice. If such oxygen does chill the baby, I should not want to give it.

DR. C. ANDERSON ALDRICH, Rochester, Minn.: The point is that oxygen is put through ice routinely in many places. It probably should not be done, however. Another question: Clinically, can one differentiate the anoxia of cyanosis and atelectasis from that caused by cerebral hemorrhage? Can one use the response to oxygen as a diagnostic test for the cause of the cyanosis?

DR. STEWART H. CLIFFORD, Boston: The only way I know of to differentiate the etiologic causes of the various types of anoxia that Dr. Aldrich referred to is by the process of elimination. When a baby is anoxic and cyanotic, and on examination his chest is flat to percussion and retracting, the lungs are undoubtedly the cause, particularly when the diagnosis can be substantiated with roentgenographic examination. At the same time, if pathologic lesions of the lung and cerebral injury also are present, because anoxia affects the entire body and does not limit itself to the lungs or to the brain or to some particular tissue, as part of the examination the central nervous system must be investigated.

If the results of the examination of the lungs in this cyanotic baby are negligible, then congenital heart disease or intracranial hemorrhage may be present. A congenital cardiac malformation may or may not produce a murmur, and the roentgenogram may or may not be of aid, so that study of this sort does not help in differentiation. The next step is to do a lumbar puncture; with evidence of frontal pressure and signs of intracranial hemorrhage, the diagnosis is intracranial hemorrhage with or without other pathologic changes.

With regard to the question of using oxygen as a test material, I have never been able to do that because a cleancut case of anoxic anoxia without a great deal of stagnant element is seldom seen, and at this stage congenital mal-

formation of the heart is usually combined with other pictures or complicated with cardiac or even with noncentral nervous system elements. As a diagnostic test, I have not had much success through the use of oxygen.

Panel Question.—In the expectant treatment of atelectasis, is the use of penicillin or of the sulfonamide drugs advised to prevent pneumonia?

Dr. Stewart Clifford, Boston: My associate and I have a definite policy on that. The incidence of atelectasis, if one is looking for it and makes a careful examination on all newborn babies, is high. We believe 80 or 90 per cent of these babies will recover spontaneously with conservative treatment. If there has been no evidence of prolonged rupture of membrane or infection in the mother, these babies are allowed to go along without any prophylactic treatment.

If there has been rupture of the membrane or a history of infection in utero, the baby is immediately given a combination of penicillin and sulfadiazine. If the baby goes beyond three or four days without improvement, he is also given penicillin and sulfadiazine for prophylaxis. Both must be given.

A MISCONCEPTION CONCERNING THE Rh FACTOR AND THE INTERRUPTION OF PREGNANCY

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PRESENT DAY knowledge of the Rh factor has created many problems. An example is the advisability of interrupting a pregnancy. This question arises in those Rh-negative women who have had previous erythroblastotic babies and whose husbands have been shown to be homozygous for the factor Rh. Within the past year we have seen 2 cases, both of which illustrate the fact that serologic results in such cases must be cautiously interpreted and carefully checked.

REPORT OF CASES

CASE 1.—Mrs. M. G., a 31 year old white woman, para II, gravida III, was referred to the Laboratory of the Medical College of Virginia at approximately four and a half months' gestation. Her previous history revealed that she was delivered of a normal female child in 1938 and of a full term erythroblastotic infant in 1945. The latter lived three days. At this time, March 1947, she was found to be Rh negative and to belong to group O. Her serum showed saline anti-Rh agglutinins, with a titer of 10, and incomplete antibodies of 40. No history of transfusions could be elicited. Her husband also belonged to group O and was found to be Rh_0 (DcE). Consequently, with the serums available it was impossible to determine whether he was homozygous or heterozygous. The surviving child was found to belong to group O, Rh_0 (DcE). The patient requested that the present pregnancy be interrupted. Since a definite conclusion as to the advisability of interrupting this pregnancy could not be reached from a serologic point of view, advice was sought from one of the leading authorities on the Rh factor. In the meantime, agglutinins and incomplete antibodies (bovine albumin technic) had risen to a titer of 320 (May 1947). The opinion rendered on the basis of the aforementioned observations stated that interruption of this pregnancy seemed justifiable because of the apparent homozygosity of the father and the high level and rise in antibody titer in the maternal serum. This opinion was conveyed to the obstetrician in charge. However, he informed us subsequently that the patient had changed her mind and had decided to carry through the present pregnancy.

This study was aided in part by a grant from the Virginia Academy of Science.

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Read before the joint meeting of the Section on Obstetrics and the Section on Gynecology at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 25, 1948.

A review of the previous and subsequent serologic determinations on the mother's serum gave the results noted in table 1.

On July 30, the patient went into labor spontaneously and was delivered of an apparently healthy male child, weighing 2,670 Gm. The infant's blood count was within normal limits. His red cells were shown to belong to group O, type Rh negative. Because of the possibility of blocked Rh-positive cells, a sample of the baby's blood was suspended in 20 per cent albumin and also subjected to a test with anti-human-precipitin serum,[1] both procedures giving negative results. The baby's serum contained strong incomplete antibodies.

The infant remained well and was discharged at 12 days of age. Subsequent examinations showed him to be in perfect health.

TABLE 1.—*Results of Serologic Tests in Case 1*

Date	Saline Agglutinins	Titer of "Incomplete" Antibodies (Albumin Technic)
3/17 (3½ mo. gestation)	10	40
5/28	320	320
6/12	10	320
7/ 1	0	320
7/30 Delivered normal Rh-negative child		
8/20 (21 days postpartem)	<10	320

TABLE 2.—*Summary of History in Case 2*

Date	History
1938	Premature labor after 5 months' gestation; baby died after 36 hours
1940	Full term pregnancy; child living and well
1941	Spontaneous abortion after 2 months' gestation
1942	Full term pregnancy; child living and well
1944	Spontaneous abortion after 3 months' gestation
1946	(January) Pregnancy terminating in icterus gravis neonatorum (8½ months); died after 76 hours
1946	(November) Pregnancy terminating with stillborn erythroblastotic infant

CASE 2.—Mrs. J. W. W., a 27 year old white woman, para IV, gravida VIII, came to the Medical College of Virginia Blood Bank to donate blood. Discussion of her previous history revealed the facts noted in table 2.

In November 1946, the patient and her husband were typed by an Rh laboratory in another state, and the following report was given to the patient:

"Mrs. J. W. W. Group O Rh negative (dce)
Mr. J. W. W. Group A Rh_1 (DCe) Hr'negative (homozygous)
Serum of Mrs. J. W. W. contains no saline agglutinins but glutinins (plasma technic) of a titer of 192."

On this basis and because of the patient's statement that she was possibly pregnant at this time (January 1947), she was rejected as a blood donor. However, it was suggested that this laboratory follow her anti-Rh antibody titer throughout this

1. Coombs, R. R. A.; Mourant, A. E., and Race, R. R.: A New Test for the Detection of Weak and "Incomplete" Rh Agglutinins, Brit. J. Exper. Path. **24**:255, 1945.

pregnancy, if indeed she was pregnant. A specimen of blood taken from the patient at that time revealed the absence of saline agglutinins and presence of incomplete antibodies with a titer of 200. She was later found to be pregnant, and a review of results of the patient's previous and subsequent serologic tests gave the information noted in table 3.

Three days after the examination of September 1947, labor was medically induced, but the patient was finally delivered by a classic cesarean section because of prolapse of the umbilical cord. At the same time a sterilization procedure was carried out. The newborn female child, weighing 2,660 Gm., appeared to be in perfect health and remained so thereafter.

Examination of the cord cells in the Medical College of Virginia Laboratory showed them to belong to group A, type Rh negative, with a negative reaction to the test with anti-human-precipitin serum, demonstrating the absence of an antibody coating.

It is of interest to note that early in her last pregnancy the patient was advised by two of the physicians in her city to have the pregnancy interrupted. She refused to do so. In August when the patient had a titration done on her serum by the same out of state laboratory that furnished the original report, she

TABLE 3.—*Summary of Results of Serologic Tests in Case 2*

Date	Laboratory	Saline Agglutinins	Titer of "Incomplete" Antibodies
11/46	B. Rh Laboratory	0	192 (plasma technic)
1/47	Medical College of Virginia	0	200 (albumin technic)
5/47	Medical College of Virginia	80	320 (albumin technic)
8/1/47	B. Rh Laboratory	0	768 (albumin technic)
9/7/47	Virginia Blood Bank	0	128 (plasma technic)
9/14/47	Virginia Blood Bank	0	128 (plasma technic)
9/17/47	Virginia Blood Bank	0	128 (plasma technic)
9/24/47	Virginia Blood Bank	0	32 (plasma technic)
9/27/47	Normal Rh-negative child delivered		
12/47	Approximately 6 weeks post partum	0	128 (albumin technic)

was also seen by a prominent obstetrician who remarked that had he seen the patient earlier he would have strongly advised interruption of this pregnancy because of the rising antibody titer and the husband's homozygosity.

Unfortunately, we neglected to check the reaction of the husband's cells with anti-Hr′ (anti-c) serum at the time the patient came to our attention. Several weeks after the last delivery and sterilization of the patient we tested the husband's cells and found them to be group A, type Rh_1 (DCe) Hr′ (c) positive, indicating his apparent heterozygosity.

COMMENT

The first case (M. G.) showed a rather definite increase and qualitative change in antibody titer, which in the minds of many investigators are indications of active immunization. As an anti-d serum was not available to us, the genotype of the Rh_2 (DcE) husband, in reference to the clinically important D antigen, could not be determined. Although the chances were in favor of another Rh-positive child, on the basis of the first Rh-positive child, the second erythroblastotic and undoubtedly Rh-positive child and the rising antibody titer, this pregnancy terminated in a live Rh-negative infant.

In the second case (J.W.W.) the antibody titer [2] rose and slowly fell during the pregnancy, regaining a somewhat higher level six weeks after delivery. The husband's genotype was erroneously determined as homozygous; on this basis, as well as on that of the history and the antibody titers, interruption of pregnancy was strongly suggested, and sterilization was actually carried out.

Both cases show an increase and a qualitative change in anti-Rh antibodies, despite an Rh-negative product of conception. This simulates closely the phenomenon of nonspecific anamnestic reaction. Although attention was called to this phenomenon by several authors [3] throughout the literature on the Rh factor, its existence was seriously questioned in a recent article by Wiener and associates.[4] The opinion expressed in this article ascribed such a reaction to "the intrinsic inaccuracies of titration methods." However, in the cases reported here the titrations were checked by multiple methods and the height of the titers almost preclude gross errors.

In each case physicians favored interruption of the pregnancy, an opinion based on serologic data. In the second case we neglected to check the anti-c reaction of the husband at an early date. Had this been done, confusion created by an erroneous laboratory report could have been avoided.

SUMMARY

Two cases illustrating the danger of interrupting pregnancy in the immunized Rh-negative woman because of the history of previous erythroblastotic children and the supposed homozygosity of her husband are reported. Cautious interpretation and careful recheck of the serologic results in all cases of Rh sensitization, and particularly in those involving the zygosity of the husband, are urged.

Dr. W. T. Moore, Dr. T. R. Mack and Dr. J. H. Scherer cooperated in the study of these cases.

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2. Although the titration values were obtained by different laboratories and different technics, it should be pointed out that the results obtained by the Virginia Blood Bank, and by us (Medical College of Virginia), were rechecked by us with the precipitin technic and found to correspond with variations of one dilution. The procedures used in the original titrations by both laboratories are those standardized by the National Institute of Health (December 1946).

3. Potter, E. L.: Rh, Its Relation to Congenital Hemolytic Disease and Intragroup Transfusion Reactions, Chicago, The Year Book Publishers, Inc., 1947, p. 130. Levine, P.: Mechanism of Isoimmunization by the Rh Factor of Red Blood Cells: Standardization of Anti-Rh Serums, Arch. Path. **37**:83 (Feb.) 1944. Page, E. W.; Hunt, M., and Lucia, S. P.: The Antepartum Prediction of Hemolytic Disease of the Newborn, Am. J. Obst. & Gynec. **52**:794, 1946.

4. Wiener, A. S.; Wexler, I. B., and Shulman, A.: Therapy of Severe Erythroblastosis Fetalis with Repeated and Massive Exchange Transfusions, Am. J. Clin. Path. **18**:141, 1948.

DISCUSSION

DR. S. A. COSGROVE, Jersey City, N. J.: Dr. Kendig and his associate have shown the fallacy of the hysteria which would apply so-called therapeutic abortion to every pregnancy in which there was a chance of unfortunate outcome in relation to the health and survival of the fetus concerned. Some years ago, certain differences in experimental phenomena in various human bloods led to the assumption of substances in some bloods which other bloods did not show. This hypothesis was as valid as many others which have proved of clinical usefulness. It has been usefully related to certain previously inexplicable transfusion phenomena, and to fetal erythroblastosis and related clinical conditions. But as time has gone on, variation in the primary phenomena on which the original hypothesis was based has necessitated more and more complex additions to the simple hypothesis first evolved, and more and more variation in the number and variety of laboratory procedures employed. This necessarily increases the liability of error in either the laboratory findings or the clinical application thereof, or both. The homozygosity, or heterozygosity, of the Rh-positive father is frequently difficult to determine with certainty. The cases presented by Dr. Kendig substantiate this fact. Furthermore, abundance of actually observed and deductive statistics indicates the probability of much physiologic variability. Bloxsom estimated that 13 per cent of all matings involve Rh-negative mothers and Rh-positive fathers. On probable proportions of homozygosity and heterozygosity and the assumption of equal numbers of offspring in large material, about 9 per cent of all fetuses might be endangered by incompatibility of blood in the parents. But actual incidence of hemolytic disease from this cause does not even approach such fantastic estimations. Instead of 1 in 11 births, actual incidence from several sources ranges from 1 in 200 births to 1 in 500. Both Potter's incidence and that of my associates and me fall within this range. Not all these babies die, of course, and there is constant improvement in their treatment, so that in a recent series of more than 9,000 births we actually lost 1 of 470 babies. This potential is much less than the risk of loss from spontaneous abortion and but little more than twice the risk of mongolism, hardly greater than that of hydrocephalus.

In other words, there is no more justification for aborting a pregnancy because of Rh incompatibility of the parents, even when strong laboratory evidence of high risk to the baby is present, than there is for aborting all pregnancies because of the possibility of fetal loss from a large variety of other risks.

DR. JOHN C. HUGHES, Pittsburgh: This excellent presentation and discuscussion by Dr. Kendig and Dr. Cosgrove highlights the whole complex problem of the obstetric management of the Rh-immunized mother. I should like to reemphasize the following points:

1. The height of the titer of an immunized mother bears no direct relation to the degree of fetal damage.

2. In the light of recent reports, it is apparent that an immunized mother with a history of a previous erythroblastotic infant may subsequently deliver a clinically normal baby.

In view of these facts, it is obvious that there is no method for predicting accurately which infant will be affected by Rh conflict. For this reason, I feel that therapeutic abortion and sterilization are unwarranted in the management of the immunized mother. A high degree of fetal salvage can be achieved by a careful conduct of labor and immediate and energetic pediatric care. It is my feeling that the immunized Rh-negative mother should receive analgesic drugs with great caution and should be delivered under local or regional anesthesia.

News and Comment

GENERAL NEWS

Physicians Certified by the American Board of Pediatrics.—The following physicians were certified as specialists by the American Board of Pediatrics after examinations held in Atlantic City, N. J., Nov. 17, 18 and 19, 1948:

Frederick Merrill Adams, Birmingham, Mich.; Reginald Anthony Allen, Providence, R. I.; William Dewey Alsever, Syracuse, N. Y.; Grace A. Altenau, Brooklyn; Perry P. Amick, Des Moines, Iowa; Oscar Randolph Batson, Nashville, Tenn.; Nina Bleiberg, Long Island City, N. Y.; Irving Frederick Burton, Detroit; Maclyn Cagan, North Arlington, N. J.; Vincent P. Casey, New York; Walter L. Cohn, Philadelphia; Edward Perry Crump, Nashville, Tenn.; William Anderson Dickson, Boston; Benjamin Dickstein, Philadelphia; Edward C. Dyer, Boston; Jane A. Erganian, Glen Rock, N. J.; Katharine W. Evans, Philadelphia; Mervin Edward Fischman, Newark, N. J.; William C. Friedman, Far Rockaway, N. Y.; Margaret Eugenia Geib, Elizabeth, N. J.; Elizabeth Alice Gregory, Arlington, Mass.; Howard Yeager Harris, Kingston, Pa.; Ruth Cameron Harris, New York; Andrew Dickson Hunt Jr., Philadelphia; Mary Elizabeth Hyman, New York; J. Hoyt Kerley, New York; Josephine Gross Kety, Philadelphia; Harold Klein, Brooklyn; Joseph C. Knox, Wilmington, N. C.; Louis L. Krafchik, New Brunswick, N. J.; Saul Krugman, New York; Martha Frances Leonard, Highland Park, N. J.; Warren D. Leslie, Wheeling, W. Va.; Ann Lublin, Detroit; Donald Fraser Lyle, Philadelphia; Lillian Marks, Columbus, Ohio; Clarice L. McDougall, Grand Rapids, Mich.; John D. McKey, Orlando, Fla.; Henry Mitchell Putnam, Dedham, Mass.; Arthur Robinson, Denver; James Harold Root Jr., Waterbury, Conn.; Jonas Samuel Rosenberg, Batavia, N. Y.; Maurice Ross, Saco, Maine; Estelle Siker, Port Chester, N. Y.; Arthur I. Sims, Arlington, Va.; Alex J. Steigman, Cincinnati; Edward Hoge Vick, Narberth, Pa.; Betty Willis Whitehead, Chatham, Va.; Milton Michael Willner, Newark, N. J.; Natalie Yarow, New York; Alex C. Zarchy, Cedarhurst, N. Y.

PERSONAL NEWS

Dr. Stanley Gibson Retires as Chief of Staff of Children's Memorial Hospital, Chicago.—Mr. John P. Wilson, president of the board of directors of The Children's Memorial Hospital, Chicago, announced on Dec. 1, 1948, that Dr. Stanley Gibson is retiring on Jan. 1, 1949 as chief of staff, having attained the normal retirement age during this current year.

Dr. Gibson will continue on the medical staff of the hospital as consulting cardiologist. He has been a member of the staff since 1932 and chief of staff since 1944.

The board of directors of the hospital has appointed Dr. John A. Bigler chief of staff, effective Jan. 1, 1949. Dr. Bigler has been a member of the medical staff since 1931, medical director of the outpatient department of the hospital from 1934 to 1944 and assistant physician in chief and medical director since 1944.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

SYNERGIC ACTION OF PENICILLIN AND SULPHATHIAZOLE ON BACTERIUM TYPHOSUM. JOSEPH W. BIGGER, Lancet **1**:81 (Jan. 19) 1946.

Sulfathiazole in a concentration of 10 mg. per hundred cubic centimeters will not sterilize a meat infusion broth culture of Eberthella typhosa (700,000 bacilli per cubic millimeter). Penicillin in a concentration of 8 units per cubic centimeter is equally ineffective. A combination of 10 mg. of sulfathiazole per hundred cubic centimeters and 4 units of penicillin per cubic centimeter sterilized the culture in each of seven strains of E. typhosa tested. In three of the strains 2 units of penicillin per cubic centimeter plus sulfathiazole was effective.

The author suggests that in cases of typhoid an attempt be made to keep the sulfathiazole and penicillin levels in the body fluids at 10 mg. per hundred cubic centimeters and 2 units per cubic centimeter, respectively. The unknown factors are (1) the in vivo synergistic action of the drugs and (2) the concentration of typhoid bacilli in the infected tissues.

HODGES, Cleveland, Ohio.

Metabolism; Infant Feeding; Milk and Other Foods

PARENTERAL NUTRITION: II. UTILIZATION OF EMULSIFIED FAT GIVEN INTRAVENOUSLY. J. M. MCKIBBIN, K. M. TERRY, JR. and F. J. STARE, J. Clin. Investigation **25**:679 (Sept.) 1946.

A fat emulsion consisting of 15 per cent refined coconut oil stabilized with purified soybean phosphatides was given to 4 dogs as daily intravenous infusions for periods of one month. The dose furnished 15 to 16 calories per kilogram of body weight per day to dogs receiving oral rations adequate in all nutritional factors but inadequate in calories.

Fat emulsion infusions prevented further loss of weight and produced increased nitrogen retention. The fat was not lost in urine and feces, nor was it stored as such in tissues, except for accumulation in the reticuloendothelial cells of the liver. Total carcass analysis for fat on 2 dogs showed that body lipids were only slightly displaced in chemical makeup toward that of coconut oil. A minimum of 0.72 and 1.56 Kg. of coconut oil could not be accounted for in the dog tissues and therefore was thought to be metabolized for energy purposes during the experimental period.

Addition of cholesterol to fat infusions produced a reversible impairment of hepatic function, as shown by increased sulfobromophthalein retention, cholesteremia and increased cholesterol content of the liver. Those functions returned to normal when fat infusions were stopped.

BRODSKY, Cincinnati.

A DIETARY SURVEY OF PREGNANT WOMEN AND OF SCHOOL CHILDREN IN EDINBURGH. M. H. ROSCOE and H. S. MCKAY, Edinburgh M. J. **53**:565 (Oct.) 1946.

This study came from the department of medicine, University of Edinburgh. The pregnant women and school children of Edinburgh stand out as more anemic than most other groups in that city. The diet of many pregnant mothers was shown to be deficient in protein and iron, because of a failure to use proper rations. Children taking a lunch to school had a noon meal much inferior to one which might be prepared at home.

NEFF, Kansas City.

Vitamins; Avitaminoses

INFANT MORTALITY RATE IN BUDAPEST IN 1945. E. FERENCZI, Orvosok lapja **2**:817 (July) 1946.

The infant mortality rate in Budapest increased in 1945 while the battle in Budapest was raging and reached as high a level as in the last years of the past century. Infant mortality had shown a constant reduction in recent years in the city. The rate was the lowest, 8.6 per cent, in Budapest in 1938, while in 1945 it grew to 26.6 per cent. If mortality rates in the various districts of Budapest are compared, the highest rate was in district I (Castle) where the rate in 1940 was 6.4 per cent, while in 1945 it increased to 27.5 per cent. The inhabitants of the Castle district were of the most cultivated and well-to-do classes, but here the battle lasted the longest and was the most violent. The lowest mortality rate appeared to be in district II of the city: 4.4 per cent in 1940 and 15.9 per cent in 1945. This is to be explained by the fact that the district fell to the Russian troops within a few hours. The most frequent causes of infant mortality were: starvation, malnutrition, atrophy and diarrheal diseases.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

Prematurity and Congenital Deformities

CONGENITAL MALFORMATIONS IN RATS INDUCED BY MATERNAL DEFICIENCY OF VITAMIN B_2. A. GIROUD and J. BOISSELET, Arch. franç. de pédiat. **4**:317, 1947.

In an attempt to reproduce Warkany's experiments, the authors submitted female rats to a synthetic diet free of vitamin B_2. The animals were bred as soon as the deficiency was thought to be sufficient. In some cases, however, small amounts of the vitamin were given in order to eliminate the first clinical signs of deficiency. After bearing their first offspring, the female rats which had been maintained on a deficient diet miscarried.

In the offspring of these rats, cleft palate, associated often with agenesis of the maxilla, was observed. Lesions of the limbs were limited to a small reduction in size.

One of the newborn rats was a monster, with thoracic ectopy of the abdominal viscera and duplication of the axial system (chorda dorsalis), the pituitary gland and the floor of the nervous system.

These results are somewhat different from those obtained by Warkany. The difference might be explained on the basis of a few variations in the diet or because of a peculiar sensitivity of the strain, which does not usually undergo such abnormalities.

MINKOWSKI, Paris, France.

HEPATIC FUNCTION OF PREMATURE INFANTS. D. VITTORIA BORI and L. BELLINI, Riv. di clin. pediat. **40**:616 (Oct.) 1942.

Two hepatic function tests were used in this study, that of Ucko and that involving the excretion of quinine sulfate. Of the premature infants 57 per cent, of undernourished full term infants 50 per cent and of healthy infants 20 per cent showed inadequate hepatic function by the Ucko test. Of the premature infants 71 per cent, of the undernourished full term infants 75 per cent and of the healthy infants none showed inadequate hepatic function by the quinine sulfate elimination test.

HIGGINS, Boston.

MOTOR FUNCTION OF THE STOMACH OF NEWBORN PREMATURE INFANTS. A. INGIULLA, Riv. di clin. pediat. **41**:149 (March) 1943.

Premature infants were observed as to the time of the beginning of the emptying of the stomach and the time of its completion after a feeding containing barium sulfate was taken.

In the first week of life emptying began usually in from ten minutes to one hour from the feeding and was completed in from eight to twelve hours. In the second week of life, emptying began in ten to twenty minutes and was completed in seven to nine hours. In the third week of life, emptying began in ten to thirty minutes and was completed in three and one-half to six and one-half hours. In the fourth week, emptying began in two to ten minutes and was completed in four and one-half to seven hours.

HIGGINS, Boston.

ROENTGENOLOGIC PICTURE IN VARIOUS FORMS OF DWARFISM. GIULIO DE GIULI and LEONARDO DUCCI, Riv. di clin. pediat. **44**:321 (June) 1946.

The authors studied, especially from the roentgenologic point of view, 10 cases of dwarfism of various pathogenetic origins.

They describe the signs on which a differential diagnosis can be based and express the opinion that from these signs, and especially from the behavior of endochondral growth, a classification of dwarfism can be formulated.

FROM THE AUTHORS' SUMMARY.

EARLY AND LATE TREATMENT OF IMMATURE INFANTS WITH ESTROGENS. F. UGARTE, Arch. argent. de pediat. **26**:29 (July) 1946.

The author summarizes his observations and reaches the following conclusions:

1. Treatment of premature babies with estrogens gives remarkable results. It should be started shortly after birth and be kept up until the end of the first year of life if the child presents abnormal manifestations related to immaturity.

2. Administration immediately after birth is followed by decrease in mortality, a distinctly favorable action on the weight curve, a beneficial effect on the thermoregulatory function and noticeable increase in immunity.

3. If the treatment is administered in succeeding months, the results are distinct improvement in general function, constant increase in weight and appetite, increasing immunity and harmonious growth.

4. Intramuscular injections every week or ten days, with a total dose of 50,000 to 80,000 units, are preferred.

The mode of action of theelin is based on the fact that prematurity causes an actual cellular and endocrine deficiency, since the physiologic stimulus for the development of the fetus is lacking.

FROM THE AUTHOR'S SUMMARY.

Newborn

RENAL INFARCT IN NEWBORN INFANTS. A. E. LARGUIA, J. E. RIVAROLA and J. R. VAZQUEZ, Arch. argent. de pediat. **26**:15 (July) 1946.

The clinical history of 2 patients is presented. The diagnosis of renal infarction is based on a tumor in the renal region, accompanied with infection, severe illness, hyperthermia, gastrointestinal symptoms (such as vomiting or diarrhea) and hemorrhagic manifestations (such as hematuria or melena). Differentiation must be made from such conditions as hematoma of the adrenal gland, hemorrhagic disease of the newborn, nephritis, pyelonephritis and pyonephrosis.

The clinical picture of renal infarction and that of hematoma of the adrenal gland are much alike. Renal infarction, because of its infectious origin, is preceded by otitis, bronchopneumonia, omphalitis and infectious diarrhea of the newborn. Hematuria is of frequent occurrence with infarction. The lesion predominates on the left side because of the circulatory conditions on that side. Physically, the tumor of the adrenal gland is larger and less movable and presents no renal ballottement.

Hemorrhagic disease in the newborn, so intimately related to hypoprothrombinemia, has multiple manifestations, easily diagnosed according to their location. The finding of a renal tumor rules out the diagnosis of acute nephritis, pyelonephritis and pyonephrosis. Differentiation from tumors of the newborn is easy, since in cases of the latter condition the general symptoms found with infarction are not present.

In severe or generalized processes the renal infarct and thrombosis may be only a complication of the main condition, and in such instances an infarct may be observed at autopsy.

ROJAS, Boston.

EPIDEMIC DIARRHEA IN NEWBORN INFANTS. GERT VON SYDOW, Svenska läk.-tidning. **42**:1708 (June 22) 1945.

In a ward in which 51 premature infants were kept there occurred, during three weeks in January 1944, 6 cases of severe diarrhea with yellow, fetid stools and acidosis. In 4 cases the disease was fatal. The sick infants were from 8 days to 2 months of age. The incubation period of the disease was six to eleven days. Immediate isolation of the sick infants in a separate ward with special nurses, who were kept from the other infants apparently halted the epidemic. This was the second occurrence of infectious diarrhea in Sweden.

WALLGREN, Stockholm, Sweden.

RELATION OF THE RH GROUP TO ERYTHROBLASTOSIS FETALIS. ARNE GAMMELGAARD, Nord. med. (Hospitalstid.) **27**:1701 (Aug. 31) 1945.

The author studied 17 cases of erythroblastosis fetalis as to the occurrence of the Rh factor. He observed that 77 per cent of the mothers were Rh negative, while all the infants and fathers were Rh positive. In 92 per cent of the mothers antibodies were demonstrated. No connection was observed between the level of antibodies in the blood and the number of infants born with erythroblastosis fetalis.

WALLGREN, Stockholm, Sweden.

PREGNANCY IN DIABETIC WOMEN. ALEXIS BROSSET, Nord. med. (Hygiea) **26**:1037 (May 18) 1945.

A study of 36 pregnancies in 27 diabetic women at the general maternity hospital in Stockholm, Sweden, from 1934 to 1943 is presented. No definite effect of pregnancy on the diabetes of the mother could be observed. In 33 cases the pregnancies ended with the delivery of living infants. Despite careful treatment of the diabetes throughout pregnancy, the prognosis for the children was poor. The mortality rate was 53 per cent. The frequency of overweight infants and of infants with congenital malformations was not great. Hypoglycemic shock was demonstrated in only 1 of the infants. Unusual attacks of cyanosis, which were occasionally fatal, occurred, possibly due to some form of cardiac failure.

WALLGREN, Stockholm, Sweden.

Acute Contagious Diseases

THE EFFECT OF CHEMOTHERAPY ON THE DURATION OF THE CARRIER STATE FOLLOWING SCARLET FEVER. A. DANIEL RUBENSTEIN and GEORGE E. FOLEY, New England J. Med. **233**:315 (Sept. 13) 1945.

The epidemiologic investigation of two small outbreaks of scarlet fever, one occurring in an orphanage and due to a type 1 streptococcus, and the other occurring in a schoolroom and due to a type 5 streptococcus, presented an opportunity

to study the effect of chemotherapeutic measures on temporary and convalescent carriers.

In both epidemics the utilization of small daily doses of a sulfonamide preparation—sulfamerazine in the first instance and sulfadiazine (Pickrell's solution; 2.5 per cent solution of sulfadiazine in 6 per cent triethanolamine) in the other—apparently reduced to a minimum the number of persons carrying the incriminated organism. Studies among the families of children who acquired scarlet fever in the outbreak in the schoolroom revealed a spread of the causative organism to a large proportion of the family contacts, with the occurrence of several secondary cases. A study of a group of untreated patients with scarlet fever showed that when discharged from isolation hospitals the majority carried the same type streptococcus that was present on admission.

In a large proportion of persons with scarlet fever treated with certain of the sulfonamide drugs a temporary period of "cultural latency" developed. In approximately half these persons, however, the original streptococcus reappeared in the cultures after an interval of one to five weeks. A study of persons treated with sulfathiazole suggests that the period of "cultural latency" has no effect on the incidence of late secondary cases. GENGENBACH, Denver.

APNEIC TYPES OF WHOOPING COUGH IN INFANTS. M. JANBON, J. CHAPTAL, G. VALLAT and L. BERTRAND, Arch. franç. de pédiat. **3**:224, 1946.

Under different designations, such as spasm of the glottis, internal convulsions and fits of asphyxia, arrests of respiration in the course of pertussis are described frequently in the literature.

In a small series of cases the authors observed three types of nervous manifestations: convulsive, tonic-clonic crises; generalized tetanoid crises accompanying apnea, and isolated apneic crises resembling laryngospasm of tetany.

It was felt that apnea could be interpreted either as a manifestation of encephalitis or as a functional disturbance of a reflex order, either of these concerning itself with involvement of the bulbar respiratory center. AMESSE, Denver.

TREATMENT OF WHOOPING COUGH WITH HIGH ALTITUDE FLIGHTS. E. MESSERI, Riv. di clin. pediat. **40**:90 (Feb.) 1942.

Beneficial results were obtained by taking infants with whooping cough in an airplane to a height of 3,000 meters (9,843 feet) for about one hour. The mother accompanied the infant on the flight. No infant with complicating bronchopneumonia was given this treatment. The literature regarding this method of therapy is reviewed, and the physiologic effects of high altitudes are discussed. HIGGINS, Boston.

EPINEPHRINE AND CHLORINE CONTENT OF THE BLOOD IN DIPHTHERIA AND THE EXANTHEMS OF CHILDHOOD. G. CADEDDU and F. CAREDDA, Riv. di clin. pediat. **41**:77 (Feb.) 1943.

The concentration of epinephrine in the blood showed an increase in about 50 per cent of the children with diphtheria studied, and a smaller increase in fewer of the children with measles and chickenpox; this elevation may signify increased medullary function or may represent diminished metabolism of the hormone. Variations in the chlorine level of the blood did not indicate a functional disturbance of the adrenal cortex. HIGGINS, Boston.

FATAL SHOCK FROM A FIRST INJECTION OF ANTIDIPHTHERITIC HORSE SERUM. ENRICO MESSERI and VITTORIO CHIODI, Riv. di clin. pediat. **43**:76, 1945.

The author describes a case in which death by shock occurred in a girl 6 years of age after a first injection of heterologous serum (antidiphtheritic). As unusual sensitization is difficult to prove, the discussion is restricted to the possibility of a spontaneous predisposition, on the basis of the so-called colloidoclastic diathesis. The physiopathologic elements which give grounds for this possibility are briefly discussed. It is considered theoretically possible that "shock" in this case was caused by the introduction of a shock-producing substance (histamine) with the serum, rather than by anaphylaxis. The responsibility of the practitioner is discussed from the medicolegal point of view. The conclusion is that he was not responsible, as in no way could he have foreseen this eventuality.

FROM THE AUTHOR'S SUMMARY.

DIPHTHERIA IN VACCINATED CHILDREN. ANSELMO CALAMARI, Riv. di clin. pediat. **43**:91, 1945.

A clinical and statistical study of the course of diphtheria in children vaccinated with diphtheria toxoid U. S. P. (Ramon's anatoxin).

The data and the observations on 1,300 children with diphtheria hospitalized in the pediatric clinic of Florence, Italy, during the period from 1939 to 1944 are thoroughly discussed. The statistical data of the department of hygiene of the commune of Florence in the years 1939 to 1942 are used for comparison. The morbidity in the vaccinated children was 0.53 per cent, while in the unvaccinated ones the incidence was 2.35 per cent; the death rate was much lower, and the clinical course was favorably influenced. Though vaccination by inhalation proved satisfactory, parenteral vaccination is preferred. To obtain the best results, it is advisable to give a third injection six months after vaccination with subsequent injections once a year.

The enormous importance of vaccination with the toxoid in curbing endemic diphtheria, when scrupulously executed with the proper technic and when universally applied, is emphasized.

FROM THE AUTHOR'S SUMMARY.

Acute Infectious Diseases

THE ACTION OF SODIUM SALICYLATE AND SULFADIAZINE ON HYALURONIDASE. FRANCISCO GUERRA, J. Pharmacol. & Exper. Therap. **87**:193 (July) 1946.

In the introduction to the report of his investigation, the author summarizes the problem as follows:

In his review on tissue permeability and the spreading factors in infection, Duran Reynals presented the literature on connective tissue permeability and its role in the spread of bacterial infection and the resulting inflammatory reaction. It was shown that in various forms of connective tissue there is a viscid ground substance, which is the final product of a secretion of the connective tissue cells. From the ground substance there has been isolated a polysaccharide, hyaluronic acid. The ground substance acts as a barrier to penetration and spread of foreign matter, but in certain circumstances this blocking action is absent and the foreign substances applied are distributed over a wider area. In bacterial and tissue cells, particularly testicular cells, there is found an enzyme, hyaluronidase, which hydrolyzes and degrades hyaluronic acid, decreasing its viscosity and allowing an increase in permeability and spread of foreign material through connective tissues. It is known that in rheumatic fever the mesenchymal tissues are especially involved, and the rapid spread through these tissues of the infecting agent and its inflammatory sequence are evidence of removal of the protective barrier of the connective

tissue ground substance. The recognized effectiveness of salicylic acid in arresting the inflammatory process and causing regression of symptoms in this disease has not been explained. As salicylic acid is not considered a bacteriostatic agent, evidence of any relation to one or other of the spreading factors is of great interest.

In the work reported, the influence of sodium salicylate on one of the spreading factors, hyaluronidase, was studied in rabbits and a comparison made with that of a bacteriostatic agent, sulfadiazine. The results form an important step in the understanding of the favorable action of salicylates on rheumatic infection. It was found that sodium salicylate inhibited the spreading effect of hyaluronidase, whereas sulfadiazine either had no such effect or, in some groups, seemed to increase it.

PILCHER, Cleveland.

BACILLARY DYSENTERY. JOSEPH F. BORG, Minnesota Med. **29**:1108 (Nov.) 1946.

Dysentery of the bacillary type, besides being one of the devastating diseases of the tropics, is an important source of morbidity in most other parts of the world because of the great migration of the armed forces. Bacteriologic studies of stools in cases of diarrheal disease already show a much higher incidence of bacillary dysentery than had been expected. These investigations also show that many patients with mild diarrhea really have bacillary dysentery. This is significant in that many of them will become carriers during their convalescence. The author states that therapy with sulfonamide drugs gives a good response. Sulfadiazine appears to be the drug of choice.

STOESSER, Minneapolis.

DYSGERMINOMA OF THE OVARY WITH WIDESPREAD METASTASES. E. P. PENDERGRASS and J. SELMAN, Radiology **46**:377 (April) 1946.

The case of an 11 year old girl with an orbital tumor representing a metastasis from an ovarian dysgerminoma is described. The head and neck of the femur and a vertebra from the lumbar portion of the spine were also sites of metastatic lesions.

ANSPACH, Chicago.

ACCESSORY URETHRAL CHANNEL: CASE REPORT. E. E. FONG, Radiology **46**:380 (April) 1946.

A urethrogram of a man, aged 27, in whom a penile sinus had been discovered revealed a normal urethra and showed that the sinus continued the entire length of the penis, ending blindly at the symphysis pubis.

ANSPACH, Chicago.

DIAGNOSTIC PROBLEMS OF ENTEROBACTERIACEAE. IVAN SAPHRA AND ARTURO CURBELO, Rev. cubana de pediat. **18**:405 (July) 1946.

The bacteriologist occupied with the isolation and classification of Enterobacteriaceae is frequently confronted with two interrelated problems: (1) whether certain organisms, isolated from the stool, urine or pus of sick or healthy subjects, human or animal, belong to one of the two species generally acknowledged as pathogenic, Salmonella or Shigella—in other words, problems of classification and taxonomy—and (2) whether organisms whose place with the generally considered "nonpathogenic" colon and paracolon bacilli and the Proteus group has been established are really harmless or are capable, under certain conditions, of causing infections.

Enterobacteriaceae form a system of intricately related organisms. There are no sharp border lines between species, groups or types on the ground of their motility, biochemistry, serology or pathogenicity. Only by the judicial employment of all these four criteria and by avoidance of overemphasis on one or several isolated features can diagnostic errors and misinterpretations be averted and a foundation be laid for better taxonomic classification, as well as a more biologic approach to the understanding of the biologic, epidemiologic and pathologic problems of Enterobacteriaceae.

KEITH, Rochester, Minn.

CLINICAL FEATURES OF MALARIA IN CHILDREN. ENRIQUE CASTELLANOS FONSECA, Rev. cubana de pediat. **18**:699 (Nov.) 1946.

One hundred and seventy-five cases of malaria in children were studied. The symptom presenting the greatest variation was fever, which was observed to have a diurnal routine in most cases. In young infants the most striking symptoms were splenomegaly and convulsions, being present in a larger proportion of such patients than of the preschool and school age groups. In the child, as in the adult, the diagnosis of malaria should be based on the presence of the plasmodium in the blood. Quinine and quinacrine hydrochloride U. S. P. ("atabrine") given by mouth are of value in the treatment of malaria in children when absorption is satisfactory and there is no urgency in administration.

KEITH, Rochester, Minn.

OXYURIS INFECTION BY THE AIR. P. VÉGHELYI, Orvosok lapja **2**:609 (May) 1946.

The difficulty of eliminating Oxyuris is well known. Véghelyi was of the opinion that infection can be carried by the air, therefore, he examined dust in flats where several infected persons were living. The dust contained ova of Oxyuris. Sticking-paper ribbons were hung up about the rooms, and five days later ova of Oxyuris were detected on these papers. Véghelyi expressed the belief that the possibility of infection via the air is established through these experiments.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

SEPTICEMIA IN CHILDREN. ARNE NJÅ, Tidskr. f. d. norsk. lægefor. **65**:300 (Nov. 1) 1945.

The author reports on 44 cases of septicemia treated at the University Clinic of Oslo, Norway, from 1925 to 1944. He emphasizes the appearance of localized edema as an important sign of sepsis. The prothrombin time is constantly increased. In 3 cases there was leukopenia, in 2 of which the blood picture was of leukemic type. These perhaps may be regarded as cases of secondary septicemia in acute leukemia. Before introduction of chemotherapy all such cases ended fatally. Of 33 patients treated, mostly with sulfonamide compounds, 11 recovered.

WALLGREN, Stockholm, Sweden.

PHENOTHIAZINE, ITS TOXIC EFFECT AND ITS INFLUENCE AS ANTHELMINTIC. ERLING RUSTUNG, Tidskr. f. d. norsk. lægefor. **65**:302 (Nov. 1) 1945.

Twenty-one children were given phenothiazine as a remedy against oxyuriasis. The total doses were 0.30 to 0.65 Gm. per kilogram of body weight. The ages of the children were 4 to 10 years. In most cases there occurred a more or less pronounced hemolytic anemia of toxic nature. In 1 case the hemoglobin concentration decreased to 50 per cent. The anthelmintic effect of the compound is unsatisfactory. The author advised against using phenothiazine by mouth.

WALLGREN, Stockholm, Sweden.

TWO SIMULTANEOUSLY OCCURRING CASES OF CRYPTOGENIC TETANUS. POUL MÖLLER, Ugesk. f. læger **107**:722 (Aug. 30) 1945.

Two children, 4 and 5 years of age, respectively, were admitted to a hospital at an interval of a few days for typical tetanus. There was no portal of infection demonstrable, but the author discusses the possibility of air-borne infection of the respiratory tract produced by a heavy wind that was blowing shortly before the manifestation of the disease. Both children were discharged in good condition.

WALLGREN, Stockholm, Sweden.

Diseases of Blood, Heart and Blood Vessels and Spleen

EFFECT OF EXERCISE UPON THE ERYTHROCYTE SEDIMENTATION RATE. WILLIAM A. BLACK AND PETER V. KARPOVICH, Am. J. Physiol. **144**:224 (July) 1945.

Five minutes of strenuous exercise in young adults produced a statistically significant increase in erythrocyte sedimentation rate at the end of five hours but no significant change either one-half hour or twenty-four hours after exercise.

NOURSE, Cleveland.

COMMUNICATION BETWEEN THE AORTA AND THE PULMONARY ARTERY. R. LUTEMBACHER, Presse. méd. **53**:577 (Oct. *27*) 1945.

An interesting case is presented in which there was an opening 10 mm. in diameter between the apposed aorta and pulmonary artery at the site of the ductus arteriosus. The patient was a man aged 20 who was admitted to the hospital because of dyspnea, peripheral edema and oliguria. His heart was enlarged, especially to the right, and the first sound was followed by a rough systole murmur, which persisted into middiastole, obliterating the second sound. The electrocardiogram showed right axis deviation, contrary to the usual appearance of the electrocardiogram of a person with persistent ductus arteriosus.

DAFFINEE, Melrose, Mass.

ACTION OF SULFONAMIDE COMPOUNDS AND STABILITY OF BLOOD SERUM IN INFANCY. Pasquale de Caprio, Pediatria **54**:279, 1946.

The author, in studying the reactions to the Takata-Ara, Ucko and Weltmann serum tests and the erythrocyte sedimentation rate, examined 10 children, to 5 of whom was given sulfapyridine and to the other 5 sulfathiazole.

The results were generally negative, and positive reactions were observed in only 30 per cent of those given the Weltmann serum test. This lack of reaction is ascribed to a generic change in the chemicophysical conditions which are the basis of serum stability.

FROM THE AUTHOR'S SUMMARY.

APLASTIC MYELOSIS AND ACUTE LEUKEMIA IN CHILDHOOD. ANGELO CHIEFFI, Riv. di clin. pediat. **44**:513 (Sept.) 1946.

The author in examining the relation between acute leukemia and aplastic anemia emphasizes the difficulty of a differential diagnosis not only from the clinical but also from the pathologic and histologic points of view. A case is described in which an absolutely certain differentiation between these two diseases was impossible, even after necroscopy.

Numerous cases of leukemia are described in the literature in which an initial period of aplastic anemia was followed by a temporary remission. Only in the final stage were the hematologic and bone marrow changes clearly leukemic. Two cases of this type are described by the author. In 1 of these, splenectomy brought temporary remission.

A careful examination of the frequently strong resemblance between aplastic anemia and acute leukemia, clinically and pathologically, and the observation of a not infrequent transition of one disease into the other bring the author to consider that these diseases are not two fundamentally different pathologic entities, as they have been considered up to now, but the expression of the same basic disease in which the aplastic and hyperplastic phenomena have probably the same genesis and the same significance.

The possible active participation of the spleen in the establishment of the aplastic syndrome and the importance of the antagonism between the lymphatic system and the bone marrow in the genesis of leukemia, according to the old theory of Nägeli and to the newer concepts of some modern American investigators, are considered.

FROM THE AUTHOR'S SUMMARY.

CONGENITAL HEMOLYTIC JAUNDICE. L. M. CUCULLÚ, J. E. RIVAROLA and S. COSSOY, Arch. argent. de pediat. **25**:270 (April) 1946.

A case of congenital hemolytic jaundice successfully treated by splenectomy is reported. A clinical summary is included. The patient has been examined periodically since the operation. The hemoglobin and erythrocyte levels have reached almost normal values.

Serum bilirubin decreased from 168 to 4.1 mg. per hundred cubic centimeters, and resistance of red cells was within normal limits after three months. The reticulocyte count came down to 0.8 per cent. The icteric tint of the skin and the mucous membranes disappeared. The thermic curve became normal. The urine no longer contained urobilin. The gastrointestinal disturbances, so frequently observed before surgical intervention, were no longer present. All these improvements were seen four months after the operation was performed.

A similar case of a patient successfully treated with splenectomy and still in good condition six years after operation is mentioned.

ROJAS, Boston.

LEDERER'S ANEMIA. S. URWITZ, Svenska läk.-tidning. **42**:692 (March 16) 1945.

A girl 10 months of age, breast fed and previously healthy, fell ill with increasing paleness, dark-colored urine and petechiae on the legs. She was first seen two days later. The afebrile skin was somewhat yellow and pale. Examination showed hematuria, but no bilirubinemia. The stools were normal. The hemoglobin concentration was 36 per cent; red blood cells numbered 2,170,000, with a color index of 0.84. White blood cells numbered 29,400, with normal differentiation count and 40,000 thrombocytes. Reticulocytes showed a maximal 45 per cent, while normoblasts were scanty. A myelogram showed pronounced toxic myelopoiesis and hyperplastic erythropoiesis. The osmotic resistance of the red blood cells was normal.

The child was treated with repeated blood transfusions. There was no enlargement of the spleen or lymphatic glands. She was discharged in good condition one month from the beginning of her illness with almost normal blood values.

WALLGREN, Stockholm, Sweden.

BACTERIAL ENDOCARDITIS TREATED SUCCESSFULLY WITH PENICILLIN. BERTIL HAMNE, Svenska läk.-tidning. **42**:1316 (May 18) 1945.

A boy 10 years of age with probable congenital malformation of the heart had subacute bacterial endocarditis produced by nonhemolytic streptococci. He was treated without success with various sulfonamide compounds and blood transfusions. After five and a half months penicillin was given by continuous intravenous

drip. During ten days 500,000 units in all were given, with rapid amelioration of the condition and disappearance of the fever and the infection of the blood stream. The boy was discharged from the hospital in good health, which was maintained at least six months later. The heart remained enlarged and hypertrophic.

WALLGREN, Stockholm, Sweden.

CYCLIC GRANULOCYTOPENIA. PREBEN PLUM, Ugesk. f. læger **107**:725 (Aug. 30) 1945.

A 10 year old boy, first seen at 2 years of age, had since that time had attacks of stomatitis occurring every third week, with high fever and granulocytopenia (white blood cells numbered about 3,000) lasting for a few days; during the intervening time his condition was normal. The decrease in the number of granulocytes began a few days before the fever, and an increase occurred a few days before the temperature reached normal. A myelogram taken during the interval showed an intense reaction in the bone marrow: there were 528 immature white cells to 100 immature red cells, while during the attack the ratio was 41 to 100. The author discusses the possibility of infectious or hormonal genesis of the disease. No therapeutic effect was obtained with liver, pentanucleotide or other medicaments.

WALLGREN, Stockholm, Sweden.

Diseases of Nose, Throat and Ear

EXTERNAL OTITIS, WITH ADDITIONAL STUDIES ON THE GENUS PSEUDOMONAS. S. B. SALVIN and M. L. LEWIS, J. Bact. **51**:495 (April) 1946.

There is a pronounced difference of opinion as to the principal etiologic organisms and the precise sources of infection in cases of disease of the auditory canal. Therefore, the authors made a study of 100 consecutive new or acute cases, in order (1) to determine the relative frequency of fungi and of bacteria as infective agents, (2) to learn of any possible relation between the severity of the condition and the type of organism isolated and (3) to provide material for further investigations on the characteristics of the principal pathogenic organism or organisms.

From 45 per cent of the patients' ears, some species of Pseudomonas was isolated. Only 16 per cent had fungi, and the rest showed a variety of bacterial types. From none of the 25 normal ears were either fungi or a species of Pseudomonas isolated.

STOESSER, Minneapolis.

OUTBREAK OF HEMOLYTIC STREPTOCOCCUS THROAT INFECTION CONTROLLED BY SULFADIAZINE. ROBERT B. LINDBERG, FRANCIS R. COYLE, GEORGE T. RICH and MILWARD BAYLISS, J. Lab. & Clin. Med. **31**:544 (May) 1946.

An outbreak of streptococcic pharyngitis, demonstrated to be caused by hemolytic streptococci of group A, was quickly brought under control with prophylactic administration of sulfadiazine. The drug, in a dose of 1.5 Gm. per day, was given to all persons in contact with patients; this therapy was combined with an intensive search for, and isolation of, all clinical patients.

WILKINSON, Galveston, Texas.

THE TYPE-TOKEN RATIO APPLIED TO INFANT SPEECH SOUNDS. ORVIS C. IRWIN and HAN PIAO CHEN, J. Speech Disorders **11**:126, 1946.

The type-token ratios of infants under 1 year of age are presented in relation to the size of the token and to the age of the infant. The type-token ratio is the

relation of the number of various categories of phonemes to the total number of speech sounds in a given sample. The data analyzed were based on samples of speech sounds obtained from infants 12 months of age and under, They were further subdivided into six age levels with a two month period as a level. The number of infants for each age level from the youngest to the oldest group was 62, 80, 75, 64 and 62, respectively. All the infants appeared to be normal. A three dimensional graph is presented which shows the interrelationship of the three variables: type-token ratio, age of infant and size of token. A description of the construction of the graph and directions for its use are outlined. In order to test the validity of the ratios, these readings were compared to corresponding values calculated from analysis. Differences between analysis and the graph are negligible.

PALMER, Wichita, Kan.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

CONGENITAL DUODENAL OBSTRUCTION: REPORT OF SIX CASES AND REVIEW OF THE LITERATURE. F. G. KAUTZ, J. R. LISA and E. KRAFT, Radiology **46**:334 (April) 1946.

Six cases of congenital duodenal obstruction in newborn infants are reported in detail. In 4 of the children there was complete atresia with no connection beyond a blind pouch of the duodenum. In 1 infant adhesions across the prepyloric portion of the stomach and the first part of the duodenum accounted for the obstruction, and in another the intestine proximal to the obstruction narrowed to an opening 1 mm. in diameter.

In the true atresias the proximal portion of the duodenum was dilated, assuming nearly the proportions of the stomach on roentgenograms made after administration of barium sulfate. In 2 cases a fibrous cord was present at the site of the obstruction, and in 2 there was no communication between the segments of bowel.

ANSPACH, Chicago.

DIVERTICULOSIS OF THE JEJUNUM AND ILEUM. MAX RITVO and PAUL J. VOTTA, Radiology **46**:343 (April) 1946.

The report comprises 25 cases of diverticulosis of the small intestine observed at the Boston City Hospital. The condition is seen primarily in middle and late adult life and is not associated with any clearly defined chain of symptoms. In 20 cases the lesion occurred in the jejunum, while in only 1 was the ileum affected. With the use of contrast mediums diverticula of the jejunum and ileum were seen to occur more frequently than was previously supposed.

ANSPACH, Chicago.

SIGNIFICANCE OF BILE PIGMENTS IN STOOLS OF INFANTS. M. A. SQUARCETTA ROMANO, Riv. di clin. pediat. **40**:65 (Feb.) 1942.

Examination of the stools of infants, especially for bile pigments, is important for the proper evaluation of the digestion of protein, fat and carbohydrate. The clinical significance of the findings in the stools of 31 infants is included.

HIGGINS, Boston.

ANOREXIA CAUSED BY A FOREIGN BODY IN THE ESOPHAGUS. HARALD SANDSTRÖM, Svenska läk.-Tidning. **42**:698 (March 16) 1945.

A girl 16 months of age suddenly began to lose her appetite and was seen two months later, as psychologic therapy had had no effect. Roentgenographic examina-

tion disclosed an unsuspected button and a coin in the esophagus, which were extracted by esophagoscopy. Later, the girl's appetite became satisfactory.

A boy 2 years of age had been treated several times because of vomiting, which was believed to be due to a nervous condition. The vomiting had decreased in intensity the last three months. Shortly before his admission to the hospital, vomiting again became severe. Roentgenographic examination showed a coin in the esophagus. The coin was removed by esophagoscopy, and the vomiting ceased immediately.

WALLGREN, Stockholm, Sweden.

TREATMENT OF TOXIC COLITIS IN INFANCY WITH BLOOD PLASMA TRANSFUSIONS. A. NÁDRAI, Orvosok lapja **1**:405 (Dec.) 1945.

Plasma transfusion was given in 250 cases of infantile enteritis, toxicosis, colitis and dysentery, with good results.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

THROMBOSIS OF THE PORTAL VEIN IN CHILDHOOD. C. UNGARI, Riv. di clin. pediat. **40**:668 (Nov.) 1942.

A boy 3 years of age was ill for seven months with mild fever, obstructive jaundice, abdominal pain, nosebleeds, enlarged liver, caput medusae and pronounced ascites with a transudate. He began to recover from the critical illness after being given a mercurial diuretic. A diagnosis of thrombosis of the portal vein was made. Seven months after leaving the hospital, he showed apparently complete recovery.

HIGGINS, Boston.

Diseases of the Ductless Glands; Endocrinology

THE EXPERIMENTAL PRODUCTION OF EXOPHTHALMOS IN FUNDULUS BY MEANS OF ANTERIOR PITUITARY EXTRACTS. ALEXANDER ALBERT, Endocrinology **37**:389 (Dec.) 1945.

Exophthalmos can be produced in a minnow called Fundulus within a few hours after the injection of small amounts of pituitary extract from sheep.

The reaction is due to a specific constituent of the pituitary, either the thyroid-stimulating hormone, or a new substance showing properties thus far similar. The experimental exophthalmos in Fundulus is probably not dependent on the thyroid, since the reaction occurs many hours before visible evidence of thyroid activation is obtained. Thyroid extract and thyroxin are ineffective in inducing proptosis. The hypophysis is likewise unessential, as is the presence of a functional sympathetic system. The mechanism of exophthalmos in Fundulus is conceived as the secretion of fluid by the orbital tissues into the retrobulbar space.

JACOBSEN, Buffalo.

THE ROLE OF THE ADRENALS IN THE PRODUCTION OF NEPHROSCLEROSIS BY ANTERIOR PITUITARY PREPARATIONS. C. E. HALL, P. DONTIGNY, E. BELAND and H. SELYE, Endocrinology **38**:296 (May) 1946.

It has been shown that the synthetic component of the adrenal cortex, desoxycorticosterone acetate, produces pronounced renal and cardiovascular lesions in a variety of animal species. Sensitivity to such treatment is increased if the animals are unilaterally nephrectomized and kept on a high intake of sodium chloride. The lesions consist of nephrosclerosis, periarteritis nodosa and nodules in the heart resembling Aschoff bodies. The development of these lesions is inhibited by the administration of acidifying salts, such as ammonium chloride.

The authors report that lyophilized material from the anterior pituitary gland induces nephrosclerosis, cardiac lesions and enlargement of the adrenal cortex in unilaterally nephrectomized rats kept on a high intake of sodium chloride—adrenalectomy prevents this effect.

The nephrosclerosis and cardiovascular damage caused by preparations of the anterior pituitary gland apparently are not due to a direct action of the preparation on the kidney and the cardiovascular system. It is probably mediated by the adrenal cortex, through the secretion of desoxycorticosterone-like compounds.

JACOBSEN, Buffalo.

INFLUENCE OF ADRENAL CORTICAL STEROIDS UPON THE BLOOD PRESSURE AND THE RATE OF PROGRESSION OF EXPERIMENTAL NEPHRITIS IN RATS. ABBIE I. KNOWLTON, HERBERT STOERK, BEATRICE C. SEEGAL and EMILY N. LOEB, Endocrinology **38**:315 (May) 1946.

In recent years it has been demonstrated that long-continued administration of desoxycorticosterone acetate may induce a rise in blood pressure in patients with or without disease of the adrenal glnads, as well as in normal dogs and rats. In animals treated with desoxycorticosterone acetate, this hypertension is often associated with evidences of renal damage. No similar effect on blood pressure was reported after prolonged treatment with extract of the anterior portion of the pituitary gland U. S. P.

The present study was undertaken to compare in rats the effect of desoxycorticosterone acetate and of extract of the anterior portion of the pituitary gland on the blood pressure and the velocity of progression of nephritis induced by means of a specific cytotoxic serum, which supposedly establishes renal lesions as a result of an immune response.

It was found that desoxycorticosterone acetate caused a specific renal lesion in the tubules of both normal and nephritic animals and induced hypertension. Extract of the anterior portion of the pituitary gland had no apparent effect.

JACOBSEN, Buffalo.

EXCRETION OF URINARY CORTICOIDS AND 17-KETOSTEROIDS IN THE NORMAL INDIVIDUAL. ELEANOR H. VENNING and V. KAZMIN, Endocrinology **39**:131 (Aug.) 1946.

Urinary 17-ketosteroids and glycogenic corticoids were measured in a series of normal persons.

Normal men excrete 40 to 85 units of glycogenic corticoids per twenty-four hours and normal women 25 to 65 units per twenty-four hours.

No corticoids could be detected in the urine of male infants 1 to 4 days old, but amounts of 35 to 42 units were demonstrated in the urine of 2 boys between 2½ and 3 years of age. At 5½ years, the excretion of these substances had reached values observed for men. In old age the excretion of corticoids is somewhat lower than in adult life.

JACOBSEN, Buffalo.

Diseases of the Muscles, Bones, Joints and Lymph Glands

SPONDYLOLISTHESIS: FURTHER REMARKS WITH EMPHASIS ON RADIOLOGIC ASPECTS. A. C. GALLUCCIO, Radiology **46**:356 (April) 1946.

The author describes a method of making roentgenograms of the lower lumbar portion of the spine, so that prespondylolisthesis may be recognized. The osseous defect in the posterior neural arch has been recognized in an increasing number of cases by the taking of six views. The author, while recognizing the ultimate

role played by trauma, favors a congenital defect which predisposes slipping to the anterior as the etiologic basis of the condition. ANSPACH, Chicago.

ACUTE HEMATOGENOUS OSTEOMYELITIS TREATED WITH PENICILLIN. M. AGERHOLM and J. TRUETA, Lancet **1**:877 (June 15) 1946.

The results of treatment of 30 patients are presented. Twenty-seven of these were aged 1 to 15 years, although the factor of age is not further analyzed. The authors advise 400,000 units of penicillin daily by the parenteral route. When the infection "appeared to be adequately controlled," this was reduced to 100,000 units per day. The authors advocate strongly that if pus is present at the time of the patient's admission surgical drainage with drilling of the bone be used. If this is combined with penicillin therapy, much destruction of bone will be prevented and a high percentage of primary wound closures obtained. Culture of the blood yielded organisms in one-half the cases. Culture permits rapid isolation of the organism for determination of its sensitivity to penicillin. The disease in 25 of the patients was due to Staphylococcus aureus. HODGES, Cleveland.

SO-CALLED CORTICAL OSTEOID IN CHILDREN: REPORT OF TWO CASES. P. SCHAERER, Helvet. paediat. acta **1**:395 (July) 1946.

Two cases of cortical osteoid in children are described. The cortical osteoid is a benign tumor-like change of the skeleton. It must be differentiated from sarcoma, sclerosing osteomyeltiis and syphilis. The type and genesis of the process are not yet clear. Although the possibility of a spontaneous cessation of the condition after several years is indicated, operative treatment is recommended, as the lesion disappears at once after the operation. FROM THE AUTHOR'S SUMMARY.

MUSCULAR HYPOTONIA IN CHILDHOOD. HANS ZELLWEGER, Helvet. paediat. acta **1**:427 (July) 1946.

Muscular hypotonia may be caused by diseases or by lesions in the spinal reflex center or in the supraspinal paths and centers having tonoregulatory function. The cases of muscular hypotonia observed at the Children's Hospital in Zurich, Switzerland, are discussed. Besides the well known diseases complicated by hypotonia, such as erythredema polyneuropathy (Feer's disease), chorea minor and disorders of the cerebellum, the following forms of muscular hypotonia are distinguished and illustrated with typical cases: parainfectious and postinfectious hypotonia; hypotonia as an initial symptom of a degenerative-sclerotic process of the brain; hypotonia caused by damage to, or hemorrhage into, the brain, due to birth injury or postnatal injury; hypotonia associated with congenital defects of the central nervous system; hypotonia accompanying pituitary and diencephalic disturbances, and hypotonia in children with degenerative stigmas.

FROM THE AUTHOR'S SUMMARY.

Miscellaneous

UNUSUAL EPHEDRINE REACTION. DAVID LOUIS ENGELSHER, New York State J. Med. **45**:307 (Feb. 1) 1945.

The author presents a case of ridging of the nails and extensive and prolonged dermatitis medicamentosa produced by a single therapeutic dose of ephedrine sulfate in a 14 year old patient with chronic asthma. It is his belief that this is the first case reported in the literature of ridging of the nails produced by such drug.

AIKMAN, Rochester, N. Y.

LIPODYSTROPHY AND HEPATOMEGALY,. WITH DIABETES, LIPEMIA AND OTHER METABOLIC DISTURBANCES. R. D. LAWRENCE, Lancet **1**:724 (May 18) 1946.

A detailed history of an apparently unique syndrome, occurring in a young woman, is presented. Its interest lies in its relation to the less complex types of lipodystrophy. The patient was followed for seven years, and autopsy was performed. The chief observations were: (1) lipodystrophy, i. e., complete absence of subcutaneous and retroperitoneal fat at autopsy; (2) portal cirrhosis of the liver; (3) duct proliferation in the parotid glands causing enlargement; (4) insulin-resistant diabetes with absence of ketosis and with a pathologically normal pancreas; (5) variable lipemia apparently dependent on the blood sugar level; (6) a high metabolic rate (+ 170 per cent) not due to thyrotoxicosis, and (7) no evidence that the hepatic glycogen was abnormal.

HODGES, Cleveland.

ORAL ADMINISTRATION OF PENICILLIN TO INFANTS. J. L. HENDERSON and I. W. J. MCADAMS, Lancet **1**:922 (June 22) 1946.

The authors studied a series of 37 infants. Twenty-eight were 1 month or less of age. Four were born prematurely. All but 3 were healthy, normal infants. The sodium salt of penicillin was administered in the first ounce (30 cc.) of a milk feeding. Serums were tested against a standard strain of Staphylococcus aureus.

Adequate bacteriostasis in the serum was obtained for as long as fifteen hours after the administration of 100,000 units and for six hours after 10,000 units; 5,000 units gave an adequate response in premature infants. There was some indication that absorption was better during prematurity and the first month of life than in older infants. It is suggested that this increase might be due to low gastric acidity or low intestinal content of organisms producing penicillinase during the first month of life.

HODGES, Cleveland.

ADVANCES IN PEDIATRICS. NORMAN B. CAPON, Practitioner **157**:256 (Oct.) 1946.

The author discusses briefly recent medical advances applicable to pediatrics. The prevention and control of infection in general; immunization; penicillin, indications for its use and dosages; subdural hematoma, particularly in the first six months of life; cerebral palsy; disorders of hearing and vision, stressing careful study of each individual case followed by close cooperation of physician, psychologist, teacher and the various therapists; functional disturbances, and disorders of protein metabolism with amino acid therapy are briefly dealt with in this article.

A pertinent point is well made concerning breast milk banks. Dynski-Klein (1946) suggested that every maternity unit may be regarded as an ideal background for the creation of an efficient breast milk service. The advantages are as follows: daily routine in collection and preparation is simple, no special staff or financial measures are needed, the donors are on the spot, medical control is easy, possibilities for adulteration and contamination of milk are excluded and the supply is continuous and adaptable to the demand and could be extended to outpatients.

FERDINAND, Peoria, Ill.

Book Reviews

The Rh Factor in the Clinic and the Laboratory. Edited by Joseph M. Hill, M.D. and William Dameshek, M.D. Price, $4.25. Pp. 192, with illustrations. New York: Grune & Stratton, Inc., 1948.

This monograph, a special issue of *Blood, The Journal of Hematology,* represents a series of papers on the various aspects of the Rh factor presented at the International Conference on Hematology and the Rh Factor in Dallas, Texas, and México, D. F., Mexico, in 1946. All are authoritative and stimulating presentations contributed by recognized leaders in their respective fields.

The first paper concerns itself with a survey of the significance of the Rh factor written by Philip Levine, a former pupil of Karl Landsteiner, the pioneer in the immunologic aspects of blood and red cell factors. This is a comprehensive but terse presentation documenting 100 contributions to the subject, including the author's own basic work.

The next is by R. R. Race, of the Lister Institute, an authority in the field of genetics, on the Rh genotypes and a discussion of Fisher's theory. William Dameshek, one of the editors, contributes a discussion of hemolytic mechanisms, a subject on which he has written so lucidly in previous articles in medical literature. Guzman, of Mexico City, discusses some generalities on the nucleolar content of some blood cells. This paper deals with the cytophysiology of various blood cells, lymphocytes and nucleated red cells. The interrelationship of the Rh system and the AB system is discussed in a paper by Ernest Witebsky. Joseph Hill and Sol Haberman present the evidence justifying three classes of Rh antibodies based on their reactivity. The same authors collaborate with Muirhead and Haley in the following chapter on acute renal insufficiency due to incompatible transfusion and other causes. Management is stressed in this well documented presentation.

Israel Davidsohn, of Chicago, discusses Rh antibodies, correlating the immunologic features with the clinical findings. Bruce Chown, of Winnipeg, Manitoba, Canada, takes up practically certain variations one sees in cases of erythroblastosis. Sixty selected cases with complete data are presented. Orozco, of Mexico City, in a short article considers the A and B factors a possible cause of erythroblastosis. Harry Wallerstein, of New York city, discusses the treatment of erythroblastosis by substitution transfusion.

The last two papers are devoted to a discussion of several current problems regarding the Rh factor and a historical review of blood transfusion in Mexico by Dr. Guerola, which is most interesting.

It is doubtful whether a collection of more authoritative data on the various aspects of the Rh factor and erythroblastosis fetalis exists in one volume. The material presented is current, well documented and illustrated, clearly written and concise. It is well indexed and supported with ample bibliography and original data. The papers are well integrated and, for so controversial a field, acrimony is at a minimum. The volume is highly recommended for the medical library, the hematologist, the immunologist and the clinician who is interested beyond the clinical aspects of the subject. Pediatricians and obstetricians should have this volume in their personal libraries.

Directory of Pediatric Societies *

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

Sixth International Congress of Pediatrics

President: Prof. Guido Fanconi.
American Committee:
President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.
Place: Zurich, Switzerland. Time: July 24-28, 1950.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana, Cuba.

International Union for Child Welfare

President: Mrs. Gordon Morier.
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Associação Paulista de Medicina, Secçaõ de Pediatrias

President: Dr. Armando de Arruda Sampaio.
First Secretary: Dr. Luis Fontoura y Lauro Machado Oliveira, Caixa Postal 2103, São Paulo, Brazil.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

British Paediatric Society

President: Dr. H. T. Ashby, 13 St. John St., Manchester, England.
Joint Secretary: Prof. Alan Moncrieff, Hospital for Sick Children, Great Ormond St., London W. C. 1.
Place: Windermere.

Chinese Pediatric Society

President: Dr. W. S. Fu, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Secretary: Dr. T. F. Su, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Time: Concurrent with the annual conference of the Chinese Medical Association.

Danish Pediatric Society

President: Prof. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjørup, Dronning Louises Børnehospital, Copenhagen.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

NEDERLANDSCHE VEREENINGING VOOR KINDERGENEESKUNDE

President: Dr. J. L. Keyzer, 114 St. Josephstr., Tilburg.
Secretary: Dr. H. Reerkink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASES IN CHILDREN

President: Prof. J. M. Smellie, 5 Flat, 8 Bolingbroke Grove, London S. W. 11.
Secretary: Dr. Mary Wilmers; Dr. R. Bonham Carter.
Place: 1 Wimpole St., London W. 1. Time: Fourth Friday of each month, 4:15 p. m.

SCHWEIZERISCHE GESELLSCHAFT FÜR PÄDIATRIE

President: Prof. Dr. A. Hottinger, Petersplatz 12, Basel.
Secretary: Dr. F. Hauser, Kinderspital, Basel.

SOCIEDAD BOLIVIANA DE PEDIATRIA

President: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Secretary: Dr. Cecilio Abela Deheza, Bolivia.
Place: S. C. I. S. P. Bldg. Time: Every Thursday.

SOCIEDAD CHILENA DE PEDIATRIA

President: Mr. Raúl Matte, Santiago, Chile.
General Secretary: Dr. Mariano Latorre, Santiago, Chile.
Place: Medical Society, Santiago, Chile. Time: 7:30 p. m., weekly.

SOCIEDAD CUBANA DE PEDIATRIA

President: Prof. Agustin Castellanos.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: 9 p. m., last Wednesday of every month.

SOCIEDAD DOMINICANA DE PEDIATRIA

President: Dr. Alberto Peguero, Avenida Bolivar 117, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Jaime Jorge, Lea de Castro 19, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Friday of every month.

SOCIEDAD ECUATORIANA DE PEDIATRIA

President: Dr. Alfredo Ceballos Carrión.
Secretary: Dr. Rafael Compte Andrade, P. O. Box 3480, Guayaquil.
Place: Hospital Central. Time: 11:30 a. m., every Friday.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Jesus Avarez de los Cobos.
Secretary: Dr. Luis Torregrosa F.
Place: Hospital Infantil. Time: Last Thursday of every month.

SOCIEDAD DE PEDIATRÍA DE CONCEPCIÓN (CHILE)

President: Dr. Raúl Ortega A., Hospital Clínico Regional, Concepción.
Secretary: Dr. Fidel Urrutia, Hospital Clínico Regional, Concepción.
Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., Second Tuesday of every month from April to December, inclusive.

SOCIEDAD DE PEDIATRÍA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Albino F. Dottori, Dean Fumes 2000, Esq. Ocaña (N.), Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Fumes 2000, Córdoba, Argentina.
Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiagó de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Pastor Oropeza, Caracas.
Secretary: Dr. Guillermo Flores, Chacin, Sur 17, no. 26-2, Caracas.
Place: Hospital Municipal de Niños, Caracas. Time: Once a Month.

SOCIEDAD YUCATECA DE PEDIATRIA

President: Dr. José Lavalle, Yucatan, Mexico.
Secretary: Dr. Francisco Solís, Yucatan, Mexico.
Place: Hospital del Niño, Yucatan, Mexico.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. G. Heuyer, 1 Ave. Emile Deschanel, Paris 7e, France.
Secretary: Dr. Maurice Lamy, 94 rue de Varenne, Paris 7e, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. Basil Melle, 89 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.
Secretary-Treasurer: Dr. Seymour Heymann, 17 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Dr. R. Hybbinette, Kommendorsgatan 3, Stockholm.
Secretary: Dr. B. Broman, Eriksbergsgatan 1A, Stockholm.
Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Héctor C. Bazzano.
Secretary: Dr. José M. Portillo.
Place: Club Medico del Uruguay, Avenda Agraciada 1464 (Piso 13), Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Woodruff L. Crawford, 321 W. State St., Rockford, Ill.
Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.
Place: Atlantic City, N. J. Time: June 6-10, 1949.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Warren R. Sisson, 319 Longwood Ave., Boston 15.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Atlanta, Ga. Time: April 13-15, 1949.
Annual Meeting: Place: San Francisco. Time: Nov. 14-17, 1949.

AMERICAN HOSPITAL ASSOCIATION, MASSACHUSETTS HOSPITAL ASSOCIATION

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Valjean Cooke, 8700 Argyle Ave., St. Louis.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.
Place: Atlantic City. Time: May 3-5 (?), 1949.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. P. E. Williams, 193 James St. S., Hamilton, Ontario.
Secretary-Treasurer: Dr. R. L. Denton, 1615 Cedar Ave., Montreal.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Sidney Farber, 300 Longwood Ave., Boston.
Secretary: Dr. Robert Ward, Bellevue Hospital, New York 16.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Spencer Snow, 75 S. Main St., Salt Lake City.
Secretary-Treasurer: Dr. Esther Gross, 202 E. South Temple St., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. Howard W. Brayton, 179 Allyn Street, Hartford 3, Conn.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. Clarence L. Lyon, 407 Riverside Ave., Spokane 8, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. Paul Bancroft, 909 Sharp Bldg., Lincoln, Neb.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. William D. Rothwell Jr., Republic Bldg., Denver.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Children's Hospital of the Colorado General Hospital. Time: Monthly from October to June.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. Carroll M. Pounders, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. W. A. Daniel Jr., 115 S. Union St., Montgomery 5, Ala.
Secretary-Treasurer: Dr. D. B. Monsky, 905 Norman Bridge Rd., Montgomery 6, Ala.
Place: Montgomery, Ala. Time: September 1949

ARIZONA PEDIATRIC SOCIETY

President: Dr. Hugh Thompson Jr., 110 S. Scott St., Tucson, Ariz.
Secretary: Dr. James R. Sickler, Physicians Bldg., Tucson, Ariz.
Place: Phoenix or Tucson. Time: On call.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Alice Potter, 1418 Ninth Ave., San Francisco 22.
Secretary: Dr. Carl Erickson, 595 E. Colorado, Pasadena.
Place: Los Angeles. Time: April 1949.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Edgar W. Stephens, 910 Harvey Bldg., West Palm Beach.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Lee Bivings, 20 Fourth St. N. W., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. H. L. F. Locke, 179 Allyn St., Hartford, Conn.
Secretary: Dr. L. W. Minor, 119 Main St., Middletown, Conn.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. George L. Drennen, Jacksonville, Ill.
Place: Palmer House, Chicago. Time: May 10-12, 1949.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Charlotte Fisk, 1201 Equitable Bldg., Des Moines 9.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bdg., Davenport.
Place: Des Moines. Time: April 1949.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. William C. Rivenbank, 1448 Louisiana Ave., New Orleans 15.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.
Place: New Orleans. Time: May 7, 1949.

MEDICAL SOCIETY OF THE STATE OF NEW YORK, PEDIATRIC SECTION

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. Waldo E. Nelson, Temple University, Philadelphia 40.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. H. J. Lewis, 2956 Biddle Ave., Wyandotte.
Secretary: Dr. Robert H. Trimby, 122 W. Hillsdale, Lansing.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Place, Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. George Clark, 1817 Vinton St., Omaha.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: Children's Memorial Hospital. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW JERSEY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Robert E. Jennings, 117 Washington St., East Orange.
Secretary: Dr. Israel J. Wolf, 231 E. 31st St., Paterson.

New Mexico State Pediatric Society

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

North Carolina Pediatric Society

President: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.
Secretary: Dr. Charles H. Gay, 1523 Elizabeth Ave., Charlotte, N. C.

Northern California Pediatric Society

President: Dr. William C. Deamer, 3 Fifth Ave., San Francisco 18.
Secretary: Dr. A. L. Gleason, 1066 Longridge Rd., Oakland 10.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

Oklahoma State Pediatric Society

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

Philippine Pediatric Society

President: Dr. Alberto V. Tupas, Department of Pediatrics, College of Medicine, University of the Philippines, Manila, Philippines.
Secretary: Dr. Artemio P. Jongco, Department of Pediatrics, College of Medicine, University of the Philippines, Manila, Philippines.
Place: Philippine General Hospital. Time: Every two months.

South Carolina Pediatric Society

President: Dr. B. Owen Ravenel, 95 Rutledge Ave., Charleston 16.
Secretary-Treasurer: Dr. John R. Harvin, 206 N. Sumter St., Sumter.

Tennessee Pediatric Society

President: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Secretary-Treasurer: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Place: Chattanooga. Time: Second Monday in April.

Texas Pediatric Society

President: Dr. John K. Glen, 4412 Montrose St., Houston.
Secretary-Treasurer: Dr. James N. Walker, 3616 Tulsa Way, Fort Worth 7.
Place: San Antonio. Time: Oct. 7-8, 1949.

Virginia Pediatric Society

President: Dr. C. P. Brown, 142 W. York St., Norfolk.
Secretary: Dr. E. Berkeley Neal, 303 Washington Ave. S. W., Roanoke.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Thomas G. Folsom, 1139 Fourth Ave., Huntington.
Secretary: Dr. Warren J. Parsons, 425 Eleventh St., Huntington.

Wisconsin State Medical Society, Section on Pediatrics

Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary: Dr. L. M. Simonson, 1001 N. 8th St., Sheboygan.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. John Hart Davis, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Francis F. Silver, 9400 Euclid Ave., Cleveland.
Place: Allen Memorial Medical Library. Time: 8:15 p. m., October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. A. L. Chute, 170 St. George St., Toronto, Canada.
Secretary: Dr. John Fletcher, 262 St. Clair St. W., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

BALTIMORE CITY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Charles O'Donovan Jr., 5 E. Read St., Baltimore .
Secretary: Dr. T. Campbell Goodwin, 16 E. Biddle St., Baltimore.

BRONX PEDIATRIC SOCIETY

President: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Secretary: Dr. William A. Schonfeld, 211 W. 106th St., New York 25.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Walter R. Coles, 604–2d St., Brooklyn.
Secretary: Dr. Bernard Benjamin, 845 Park Pl., Brooklyn 16.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October and November.

BUFFALO PEDIATRIC SOCIETY

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. T. Wood Clarke, 7 Cottage Place, Utica.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Tuesday of April and October.

CHICAGO PEDIATRIC SOCIETY

President: Dr. John L. Reichert, 1791 Howard St., Chicago 26.
Secretary: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

CINCINNATI PEDIATRIC SOCIETY

President: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Secretary: Dr. William F. Hunting, 6048 Montgomery, Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

DALLAS PEDIATRIC SOCIETY

President: Dr. Guy Hacker, 5711 Goliad St., Dallas.
Secretary-Treasurer: Dr. George R. Branch, 4325 Cole Ave., Dallas.
Place: Children's Hospital of Texas and Bradford Memorial Hospital. Time: 1 p. m., third Saturday and 8:30 p. m., the first Tuesday of each month.

DETROIT PEDIATRIC SOCIETY

President: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2.
Secretary: Dr. S. S. Bernstein, 650 Maccabees Bldg., Detroit.
Place: Variable. Time: Five times annually.

FORT WORTH PEDIATRIC SOCIETY

President: Dr. Frank Cohen, 712 S. Henderson, Fort Worth, Texas.
Secretary: Dr. H. H. Womack, 1422 Pennsylvania, Fort Worth, Texas.
Place: Welch and West Restaurant. Time: Third Friday of each month.

HONOLULU PEDIATRIC SOCIETY

President: Dr. Donald Marshall, Medical Group, Honolulu.
Secretary-Treasurer: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu

HOUSTON PEDIATRIC SOCIETY

President: Dr. Edward O. Fitch, 3720 Fannin St., Houston, Texas.
Secretary: Dr. Thomas J. Donovan, 3506 Sunset Blvd., Houston 5, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., last Tuesday of each month.

KANSAS CITY (MISSOURI) PEDIATRIC SOCIETY

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Hoel Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

KNOXVILLE-OAK RIDGE PEDIATRIC SOCIETY

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

LOS ANGELES COUNTY MEDICAL ASSOCIATION, PEDIATRIC SECTION

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn 16.
Secretary: Dr. Jacob J. Lichterman, 1433 Union St., Brooklyn 13.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. John Washington, 2032 Belmont Rd. N.W., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N.W. Time: Spring and fall.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. C. Barton Etter, 1678 Peach, Memphis 12, Tenn.
Secretary-Treasurer: Dr. Jacob Danciger, 188 S. Bellevue Blvd., Memphis 4, Tenn.
Place: University Center, 4 S. Dunlap. Time: 7 p. m., second Tuesday of every month.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. James Conway, 1721 E. Lake Bluff Blvd., Milwaukee 11, Wis.
Secretary-Treasurer: Dr. Walter Polacheck, 425 E. Wisconsin Ave., Milwaukee 2, Wis.
Place: City Club of Milwaukee. Time: Second Wednesday in February, April, June, October and December.

NASHVILLE PEDIATRIC SOCIETY

President: Dr. John M. Lee, Doctors Bldg., Nashville, Tenn.
Secretary: Dr. Dan S. Sanders Jr., 2103 Hayes St., Nashville, Tenn.
Time: Third Thursday of every month.

NEW YORK ACADEMY OF MEDICINE, SECTION ON PEDIATRICS

Chairman: Dr. John Dorsey Craig, 120 E. 75th St., New York 21.
Secretary: Dr. Morris Greenberg, 143 W. 87th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. Bertha M. Levy, 717 N. W. 22d St., Oklahoma City 3.
Secretary: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City 3.
Place: Oklahoma Club. Time: On call.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Milton Rapoport, 741 S. 3d St., Philadelphia.
Secretary: Dr. D. Stewart Polk, W. Montgomery Ave., Rosemont, Pa.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

Pittsburgh Pediatric Society

President: Dr. J. A. Gilmartin, 3708–15th Ave., Pittsburgh.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Municipal Hospital, Pittsburgh. Time: Second Friday in October, December, February and April.

Queens Pediatric Society

Chairman: Dr. Walter C. A. Steffen, 42-28 Union St., Flushing, N. Y.
Secretary-Treasurer: Dr. Louis Appel, 33-03 Parsons Blvd., Flushing, N. Y.
Place: Forest Hills, N. Y. Time: Third Monday of October, February, April; first Monday of December.

Richmond Pediatric Society

President: Dr. Thomas S. Chalkley, 421 W. Grace St., Richmond 20, Va.
Secretary-Treasurer: Dr. John Paul Jones, 810 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Jerome Glaser, 85 San Gabriel Dr., Rochester 10, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee.
Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Merl J. Carson, 500 S. Kingshighway, St. Louis.
Secretary-Treasurer: Dr. Jackson K. Eto, 734 Missouri Theatre Bldg., St. Louis 3.
Place: Hotel Branscome. Time: Second Thursday of each month from October to May, inclusive, 6:30 p. m.

San Antonio Pediatric Society

President: Dr. Lucius Hill, 328 Medical Arts Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Bexar County Medical Library. Time: 7:30 p. m., first Tuesday of every month.

Seattle Pediatric Society

President: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle 1.
Secretary: Dr. Jack M. Doctor, 738 Broadway, Seattle 22.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Harry F. Dietrich, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Clement H. Maloney, Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., second Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Ernest H. Watson, University Hospital, Ann Arbor.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor.

Waco Pediatric Society

President: Dr. M. C. Carlisle, 1410 Austin Ave., Waco, Texas.
Secretary: Dr. F. W. Hoehn, 1422 Austin Ave., Waco, Texas.
Place: Provident Hospital, 1725 Colcord, Waco, Texas. Time: Third Thursday of each month.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. Harry W. Kaessler, 147 Prospect Ave., Mount Vernon, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Fourth Thursday of every other month from September to June (dinner meetings).

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MAR 29

VOLUME 76 NUMBER 6

AMERICAN JOURNAL

OF

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DECEMBER 1948

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $10.00

Entered as Second Class Matter Jan. 4, 1911, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

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Manuscripts for publication, books for review and correspondence relating to the editorial management should be sent to Dr. Clifford G. Grulee, Chief Editor, Box 671, Evanston, Ill., or to any other member of the Editorial Board. Communications regarding subscriptions, reprints, etc., should be addressed, AMERICAN JOURNAL OF DISEASES OF CHILDREN, American Medical Association, 535 North Dearborn Street, Chicago 10.

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